

Rothschild vs Dainton (Contd)

MANY of those who will have listened to Lord Rothschild's speech to the Royal Society of Arts on Wednesday (see page 319) will be rubbing their hands with glee, saying that he has gone too far this time. Surely, the argument will go, it is not possible to make fun in the same speech of Lord Haldane, Professor John Archibald Wheeler of Princeton University, the proton accelerator at Batavia in Illinois and the British research councils. Is it really possible to go about mocking at respected parts of the established world of science and then persuade respectful personages such as the Permanent Secretaries of British government departments, not to mention the British Prime Minister, that the time has come for radical change in the way in which civil science is financed in Britain? The trouble is that for all the huffing and puffing which there has been in university common rooms in the past few days, there is every reason to think that Lord Rothschild's attack on the established way of things is not merely vigorous but shrewd. For one thing, there are serious flaws in the present organization of the research councils, and those who wish to defend the present system would be in a stronger position if they would confess as much. Second, there are reasons for thinking that government departments are less expert than they might be in dealing with modern problems by modern methods because of the separation between science and state first insinuated by the Haldane committee and its interpreters. Third, to choose this point in the political history of Britain for a plea for stronger control by customers of how public money is spent is likely to warm the cockles of a great many hearts in the present government, which means that Lord Rothschild is in a strong tactical position. But, finally, it is also a good time for raising afresh the question of what the contribution of scientific research to public life is meant to be. Those who pretend otherwise, and who ignore such things as the complaints of the general public about the malevolence of technology and the unwillingness of young people to enter science courses at university, are on shaky ground.

How has the scientific community been caught so obviously on the wrong foot? After all, the question of reorganization has been in the air for more than a year, and especially since Sir Solly (now Lord) Zuckerman advocated that the Agricultural Research Council should be financed from the budget of the Ministry of Agriculture. That was a shot across the bows, to say the least of it. For all the zeal with which the Council for Scientific Policy has responded, and for all the merits of Sir Frederick Dainton's report (see *Nature*, 234, 169; 1971) which eventually saw the light of day at the same time as Lord Rothschild's pronouncement, it remains a simple truth that the defence of the research councils, for what it may be worth, has been badly mishandled. First of all, the members of Sir Frederick Dainton's committee have spent much of the past year complaining that the government would not publish Sir Frederick Dainton's report. Why was none of

them willing to take the government by surprise, and agree to let the cat out of the bag? If the text of the Dainton report had found its way into print, however irregularly, before the beginning of October, its impact would have been stronger. But the document would even now carry greater weight if it made fewer compromises with the past and present. And it is unconvincing to suggest, as the Dainton committee does, that the future pattern of the research councils should be allowed to evolve under the aegis of a board including *ex officio* the President of the Royal Society no less, which would from time to time have created new research councils or have strangled others to death. Such a device is not merely a reaffirmation of the separation between government departments and scientific research which is supposed to stem from Haldane but could in principle consist of a further separation between the government and research policy. It would have been much better if the Dainton committee had grasped some of the nettles which have grown up within the research council system. Is it right that the Natural Environment Research Council should continue to exist? Should the research councils in agriculture and medicine pursue a policy of setting up research units separately from universities but without explicit connexions with the requirements of government policy? What, in any case, can be said about the scale on which these efforts should be carried out? But the Dainton report would also have been a stronger document if it had made fewer obvious concessions to the climate of opinion which has been created by the arrival of the present government in office. The arrangements suggested for liaison between the board of management of the research councils and the other government departments are, after all, in many ways incompatible with the stark interpretation of the Haldane principle. The greatest failing, however, is that even now the scientific community is for practical purposes saying nothing about the issue. Its champion is Sir Frederick Dainton and his enemy is Lord Rothschild. Sir Frederick can count on the warm friendship and fond admiration of his colleagues in the laboratory, but he will be exceedingly lucky if any of them speaks out in public.

It is therefore important to acknowledge that in some respects Lord Rothschild has indeed gone too far. First of all, his argument on the functions of scientific research is incomplete. He said on Wednesday this week that basic research has no definable function but that, of course, is quite mistaken. Even if he is right to argue that the adventitious benefits which stem from basic research have no place in the kinds of calculations which governments must make—if only governments would listen more carefully to this advice, they would less frequently be led to spend money on white elephants for the sake of what they are pleased to call spin-off—he is wrong to ignore the part that scientific research has to play in higher education. For one thing, teachers cannot teach well, and many will not teach, if they have no opportunity for research.



Second, universities which live far back from the limits of understanding tend to be unstimulating universities. Third, students cannot become creative scientists without cutting their teeth on research of the kind carried out in good university laboratories. And even if it should happen that the supply of PhDs exceeds the demand that comes simply from university teaching laboratories, not merely is there very little danger that the people concerned will finish up as lift attendants (as Lord Rothschild said) but there is no way of knowing in advance just which shiny-eyed undergraduate will turn out to be good at research. It is conventional in Britain for educationists to oppose selectivity at the age of eleven, and there is a growing tendency to complain about the rigours of university entrance, but nobody yet takes seriously the much more apparent truth that it is hard to guess at an experimentalist's flair from reading his undergraduate essays. In short, a sufficient justification for a substantial amount of basic research is that it is inseparable from higher education. Moreover, this part of the argument in defence of the research councils (or at least the Science Research Council) is in principle quantifiable. Is it entirely beyond the wit of the Council for Scientific Policy, whether it likes it or not, now cast in the role of the defender of the research councils, to do some hard thinking on this point before the date on which the government has said it will close its ears to further discussion, February 29, 1972.

Lord Rothschild is also on dangerous ground in his description of how government departments should assume the unfamiliar role of customers, with money jingling in their pockets to spend on applied research. One immediate difficulty is that the structure of government departments is necessarily inward looking. In the nature of things, Permanent Secretaries are unwilling to pay outsiders for services rendered when they can, in principle at least, provide the same services for themselves. This, after all, is why the British defence research establishments have flourished so prodigiously. What reason does Lord Rothschild now have to think that the Ministry of Agriculture will willingly spend money on research contracts with the Agricultural Research Council when it could do the same work, perhaps less well, at its own laboratories? Is there not a danger, even, that the research councils will be lumbered not with the long-range work, applied in character though it may be, which has been its stock-in-trade so far, but rather with the humdrum work which nobody particularly wants to do? In other words, there is a danger that the customer-contractor relationship, logical enough on paper, may be unworkable in practice. Certainly it could not work without farsightedness on the part of government departments of a character so far conspicuously absent, and without receptiveness on the part of the research councils, improbable now that they are all smarting from injured pride. This is why the only practical response to Lord Rothschild's document is a carefully planned experiment in research by customer-contractors. The Agricultural Research Council is the place to start. Plant breeding is an obvious subject. To suggest more than this for 1972-73 would be a folly. To agree to less would be churlish.

Lord Rothschild has also skated over thin ice in what he has to say about the character of basic science and, for that matter, the character of science. It makes for a good joke to portray the scientific community as an anarchically inclined throng of people concerned only to feather their

own nests with high flux beam reactors, proton accelerators and the like. In reality, however, there is more to be said than this. Although it is accurate to say that those who work in the more abstract branches of science such as high energy physics can be confident only that success will help them to define new problems, those who work in such remote byways are often buoyed up to do so by their awareness of how much the scientific enterprise can contribute to the general understanding and well-being of society. Professor Wheeler, of whom Lord Rothschild made fun on Wednesday, chiefly on the strength of an extract from a popular science weekly, is not merely a student of the "chemistry of geometry in superspace, where neither time nor space exist" but also the man chiefly responsible for an understanding of the way in which uranium atoms can be induced to split almost exactly (but not quite) in two. And the young men and women who have in the past and will in the future be induced to become scientists are often persuaded to do so by their recognition that their craft is in the long run beneficial. There is room for argument, quite legitimately, about the balance to be struck between basic and applied research. Most probably there has been too much of the first and too little of the second. The Science Research Council has been doing its best to put things right. But it will be to discard the baby with the bath water to create in the British scientific community such a sense of gloom that nobody cares much for research as such. That is the biggest danger in Lord Rothschild's declaration.

100 Years Ago



At the meeting of the Royal Geographical Society on Monday last, Sir Henry Rawlinson stated that the Council intended to address the Foreign Office, with a view of arranging, either directly from the Foreign Office, or through co-operation between the Foreign Office and the Society, some means of communicating with Dr. Livingstone, either by sending messengers into the interior of Africa, and offering a reward of 100 guineas to any African who will bring back a letter in Dr. Livingstone's handwriting to the sea-coast, or by organising a direct expedition, headed by some experienced and well-qualified European, who should himself penetrate to the point where Dr. Livingstone is supposed to be.

WE learn from *Les Mondes* that the lamentable disagreement between M. Daubrée, the director of the mineralogical department of the Museum of Natural History at Paris, and his assistant, M. Stanislas Meunier, is now happily terminated, and that the latter is again permitted to carry on his researches at the Museum.

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OLD WORLD

MARS

Arrival of Russians

by our Soviet Correspondent

THE safe arrival of the Soviet Mars-2 probe in an 18 h areocentric orbit on November 27, 1971, followed on December 2 by the soft landing of an instrument capsule from Mars-3, has led to self-congratulation in the Soviet press that the guidance and orientation problems which led to the failure of Mars-1 (launched November 1, 1962), and presumably Zond-2 (launched October 30, 1964), have been overcome.

Part of this success seems attributable to the use of on-board guidance systems—the orbital injection of Mars-2 was carried out without ground control, by means of an automatic device which aligned on the Sun and a star (probably Canopus). Another important factor (judging from the amount of press coverage it has obtained), the difficulty of keeping the solar batteries aligned with the Sun while simultaneously keeping the transmitting and receiving aerials pointing at Earth, has at last been resolved. (Academician A. A. Blagonravov, speaking at the Sixth Annual Meeting of the International Council of Scientific Unions' Committee on Space Research, explained that contact with Mars-1 had been lost when "a defect in the probe's orientation system resulted in a violation of the directionality of the probe's antenna to Earth".)

Less, however, has been made public about the intended experiments to be undertaken by the two probes. The TASS reports at the time of launching indicated merely that they were "to investigate the planet Mars and the neighbouring region of space and to investigate the characteristics of the solar plasma, cosmic rays and the radiation picture during the flight from Earth to Mars".

The results from the in-flight investigations are now being processed and compared with the data obtained from Cosmos satellites, Lunokhod-1 and Luna-19. Special attention has been paid to the study of the Earth's magnetic tail, and it seems (*Pravda*, December 4, 1971) that a special attempt has been made to repeat the experiments of Pioneer-7, Pioneer-8 and Mariner-4. The two Mars probes passed through the "tail region" at a distance of 20 million km (3,000 Earth radii), a distance at which Mariner-4 failed to locate traces of the geomagnetic tail. The Mars-3 readings, however, showed that for about 36 hours the distribution of charged particles with respect to velocity differed considerably from that characteristic of the solar wind—the

"most probable explanation" being that at this time the probe was passing through a region of mixing of the solar wind and geomagnetic tail, and that, therefore, the tail is still observable at this distance.

Mars-3 is also carrying the French Stereo-1 experiment, designed by Drs Steinberg and Carubos of the Meudon Observatory to study the directivity of the radiation from solar bursts. This device, mounted in the solar battery unit to ensure constant solar orientation, continuously monitors the solar radiation in the metre waveband, but, by comparing each reading with the preceding one and eliminating those which show no change, it transmits data only when actually sensing a burst. By comparing these readings with those taken at Nancy and at the Moscow Institute of Terrestrial Magnetism, Ionosphere and Radio Propagation, it is hoped to be able to map the "directivity diagram" of the bursts recorded.

The investigations to be carried out in areocentric orbit are, so far, less explicit. In a *Pravda* interview (December 3, 1971) Dr M. Ya. Marov hints, however, at a programme largely based on study of the "radiative capacity" of the planet, over a wide range, from the ultraviolet down to centimetre wavelengths. Thermal mapping of the planet is to be carried out, allowing the properties of the surface to be postulated. The chemical composition of the atmosphere is to be investigated by infrared and ultraviolet, special attention being paid to any indications of traces of nitrogen and water vapour. Important questions behind the Mars programme are: What gas predominates in the upper atmosphere of Mars? What ions are in its ionosphere? Why has Mars no magnetic screen and what are the differences in the interaction of Mars and Earth with the solar plasma? Dr Marov does not, however, indicate to what extent these questions will be answered by the two current probes.

The current Mars probes, with a mass of 4,650 kg, are more than five times heavier than the ill-fated Mars-1. One would expect, therefore, a considerable increase in the experimental capacity. Yet, in the case of Mars-2, which it now seems likely is intended for orbital survey (the hammer and sickle capsule deposited on the surface shortly after orbital injection apparently was meant merely as a symbolic gesture in case of the failure of Mars-3), with the experiments being very similar to those intended for Mars-1.

Clearly as much equipment for orbital work as possible has been placed aboard Mars-2, leaving any extras, such as Stereo-1 and of course the landing capsule, to be carried by Mars-3. Although the telemetry signals from Mars-2 and the remaining orbi-

tal section of Mars-3, as monitored by Jodrell Bank, are similar but for a greater signal strength from Mars-3 (it has not so far proved possible to monitor signals from the surface), the probes do not seem to back up each other but are complementary. This is perhaps regrettable, especially in view of the reported failure of the cameras aboard the landing capsule, but it may not only be due to a tendency of the Soviet space programme planners to avoid duplication; the question may, ultimately, be one of weight.

It has been stressed several times in the Soviet press that the new on-board computer and guidance system makes great use of micro-miniaturization, and the very emphasis on this fact, plus the apparently similar or diminished experimental capacity of Mars-2 in comparison to Mars-1, does suggest that a relatively large proportion of the weight increase of the current probe has been expended in bringing them into orbit, leaving too little available for the duplication of even the most important experiments.

PHARMACEUTICAL INDUSTRY

Beecham to Win?

IF the Glaxo shareholders agree to the recently announced bid of £290 million by Beecham for their company and if the matter is not referred to the Monopolies Commission, it seems likely that the new year will see the creation of a pharmaceutical concern which will dominate the British market and rank about tenth or eleventh in the world. But what are the factors that determine whether Glaxo is ripe for a takeover?

Certainly the announcement last month that Glaxo had suffered its first drop in profits for more than ten years is an indication that all is not well. But in the pharmaceutical industry, where the failure rate among new compounds is astonishingly high, success is often as much a matter of luck as of expenditure on research and development. And the sixteen year protection given by patents is nowadays effectively reduced to twelve years or so because of the extensive toxicological and clinical tests that are required before new drugs can be marketed.

Glaxo and Beecham are in many ways quite similar—their sales are £173 million and £182 million a year respectively and they each spend about £5 million a year on research and development. Most of the Beecham research is done at laboratories at Brockham Park, Surrey, where 25 per cent of the staff of 400 are graduates.

It was in these laboratories that the first semi-synthetic penicillins, which have formed the backbone of Beecham's ethical drug sales, were developed in

the late 1950s. There are two other smaller Beecham research laboratories—at Walton Oaks, Surrey, and Harlow, Essex. The first of these was part of the research organization of Vitamins Ltd, a company bought by Beecham in 1967, and the second was opened by Beecham itself in 1969. Most of Beecham's nutritional research is carried out at Walton Oaks and the Harlow laboratory is responsible for the synthesis and evaluation of compounds other than antibiotics.

Research at Glaxo is also conducted at three chief research centres, two of which were inherited as a result of the purchase of Allen and Hanburys and BDH Pharmaceuticals. Most of the Glaxo research is centred on Glaxo Research Ltd, Greenford, and some is also carried out by Glaxo subsidiaries in India and Italy. The planned growth of expenditure by Glaxo on research and development was spelled out by Sir Alan Wilson in the company's annual report for 1969-70. He then announced that the research and development budget would double by about 1975. Extensions to the research laboratories of Glaxo and those of Allen and Hanburys are also in hand and are expected to be completed by the middle of 1972 at a cost of £5 million.

It may be significant that about 65 per cent of Beecham's sales are of non-ethical products whereas the corresponding figure for Glaxo is 45 per cent. Glaxo has yet to show that it will reap just rewards from the £55 million which it has invested in drug manufacturing plant since 1969.

SPACE

Ionosphere Probe

EARLIER this week the latest in the Ariel series of British satellites was being prepared for launch from the Western Test Range in California on December 11. The satellite is a repetition of the previous satellite in the series, Ariel 3, but with many significant modifications and improvements. An experiment from Professor L. A. Frank's group at the University of Iowa has been added to the previous portfolio of experiments from Jodrell Bank (Professor F. G. Smith), the University of Sheffield (Professor T. R. Kaiser), the University of Birmingham (Professor J. Sayers) and the Radio and Space Research Station of the SRC (Mr R. Dalziel). An experiment from the Meteorological Office on Ariel 3 has been omitted this time.

As luck would have it, a fault connected with the EHT monitor in the guest experiment from Iowa has been responsible for a postponement from the original launch date in November, since when Professor Frank's group has been

working to ensure that the fault does not reflect a more serious problem within their experiment.

Ariel 4 was designed to provide an integrated series of experiments to study the interactions among plasmas, particles and waves in the upper ionosphere. To this end it will be placed in a 550 km orbit inclined at 83° to the equator to ensure world-wide coverage. Like its predecessor, Ariel 4 will rely on tape recording to store information until the satellite passes over a ground station. Although the tape recorder on Ariel 3 worked perfectly for 9-10 months (surpassing the previous record of 3 months for the durability of a tape recorder in space), the experimenters are aware that the recorder is the weak link in the system. Ariel 4 therefore carries two tape recorders to postpone the time when the experimenters will have only real time data available to them.

The original design has also been modified to include safeguards against interaction between the aerials of the Birmingham and Jodrell Bank experiments, which on Ariel 3 resulted in signals from the Birmingham experiment being picked up by the Jodrell Bank experiment and interfering with the collection of data.

By obtaining simultaneous observations of various aspects of the conditions in the upper ionosphere, Ariel 4 should throw some additional light on the physical processes involved in the ionosphere and magnetosphere. The Iowa experiment will examine protons and electrons between 5 eV and 50 keV, the Jodrell Bank experiment will look for radio waves which it is believed may be generated by streams of charged particles interacting with the magnetosphere and ionosphere through the Čerenkov effect, the Sheffield experiment will record ELF and VLF emissions related to the flux of charged particles as well as emissions originating from stations on the ground (which are of course influenced by the conditions in the ionosphere) while the Birmingham experiment will provide the measurements of local electron temperature and density which are essential to an interpretation of the other data. The Radio and Space Research Station is involved in both the Jodrell Bank and Sheffield experiments.

SPACE

Per Ardua ad Terminum

from *La Recherche*

No complete technical explanation for the failure of Sunday's Diamant B booster rocket seems likely in the immediate future. The Diamant B has been used successfully on three previous occasions, but a strong vibrational "pogo effect" was noticed on each

occasion and, in spite of repeated efforts to eliminate this, it proved impossible to do so. There were also defects in the Diamant B's electronic systems which helped delay this last launching, originally planned for December 2. Yet neither of these shortcomings appears to be responsible for Sunday's abortive mission.

Psychologically, the consequence of this episode is one of virtual disaster at the Centre National d'Etudes Spatiales (CNES) where the government's budgetary austerity had already introduced a note of uncertainty into the future of the French space programme. Politically, the failure of this last launching could not be more inopportune. The French government had envisaged, for some time now, imposing financial limitations on France's role in the space effort. A study group was to have examined, in January, the possibility of reducing expenses at the Guyana base, and if need be even closing down the base for several

Royal Society

PROFESSOR A. L. HODGKIN was re-elected president of the Royal Society at the anniversary meeting of the society held last week. The other officers re-elected were Sir Fredrick Bawden, Rothamsted Experimental Station, treasurer; Sir Bernard Katz, University of London, biological secretary; and Sir Harrie Massey, University of London, physical secretary. Professor K. C. Dunham, University of Durham, was elected foreign secretary.

The full council of the Royal Society for this year will consist of the officers, together with Professor E. J. W. Barrington, University of Nottingham; Professor J. W. S. Cassels, University of Cambridge; Professor A. R. Collar, University of Bristol; Dr H. M. Finnis, British Steel Corporation; Professor L. Fowden, University of London; Professor R. A. Gregory, University of Liverpool; Professor H. Harris, University of Oxford; Professor A. W. Johnson, University of Sussex; Professor R. V. Jones, University of Aberdeen; Professor R. A. Morton, University of Liverpool; Professor C. W. Oatley, University of Cambridge; Professor D. C. Phillips, University of Oxford; Mr J. D. Rose, Imperial Chemical Industries Ltd; Professor P. A. Sheppard, University of London; Professor K. Stewartson, University of London; and Professor D. H. Whiffen, University of Newcastle upon Tyne.

months each year. Next spring, the French government will be faced with the choice of continuing to build the Diamant B booster or giving up the Diamant B and buying the American Scout. CNES's future was not very bright to begin with. Since last Sunday, it is gloomier still.

AUSTRALIA

CSIRO Restrained

THE Australian Commonwealth Scientific and Industrial Research Organization spent \$A60.2 million in 1970-71, about 60 per cent of Australia's public expenditure on research and development. Although the annual report (CSIRO, Melbourne, 1971) reveals that the organization's budget was \$A8.4 million higher in 1970-71 than in the previous year, CSIRO has clearly been feeling the effects of the federal government's restrictions on public expenditure that were imposed in February this year.

The organization's building programme, for example, had to be trimmed from the \$A2.8 million originally approved to \$A1.1 million but, in spite of the cuts, work commenced on the site of the new National Standards Laboratory in Sydney and on the construction of several other laboratories. The chief project completed during the year was the new CSIRO head office building in Canberra which cost \$A1.5 million and was funded separately by the federal government.

Although 80 per cent of the income of CSIRO during 1970-71 was provided by the federal government, most of the remainder came from levies on the produce of Australia's agricultural industries—wool, meat, wheat, dairying and tobacco—which are matched dollar for dollar by the federal government.

Electron Accelerator

THE meeting of the European Committee on Future Accelerators (ECFA) in Geneva last week (see *Nature*, 234, 242; 1971) took no decision to set up a working party on the feasibility of a European Electron Accelerator. Professor A. Ashmore, director of Daresbury Nuclear Physics Laboratory, said that the committee was not in favour of starting any new project on the scale of the 300 GeV machine until that accelerator is completed. The meeting did, however, discuss the proposal in general terms and Professor Ashmore thinks it possible that a working party will be set up at the next meeting of ECFA in about six months time.

Some of the CSIRO work of particular interest to the wool industry may soon have to be curtailed because of reduced returns from the sale of wool, and the report also says that "similar difficulties may be expected to arise with others of the agricultural industry trust funds".

As well as bread and butter research and development in such fields as chemistry and physics, some parts of the organization are also engaged in work related to the needs of the Australian mineral industry. \$A3.4 million was spent on the processing and use of mineral products in 1970-71, for example, and other related research includes efforts to improve the techniques of mineral exploration and to understand more fully the disposition and mode of formation of metal ores—particularly nickel sulphide, the copper-lead-zinc ores and the ores of tin.

EQUAL PAY

No Lib Yet

THE letter from Professor David Layzer and his twenty-two co-signatories (see page 369) has raised the question whether *Nature* alone lacks a "non-discriminatory advertising code" and the probability that other newspapers and journals are refusing to publish advertisements which state that women are to be paid less than men. Telephone enquiries this week suggest, however, that those bastions of the British Empire (as was), the *Daily Telegraph* and *The Times*, do not refuse to publish advertisements which discriminate against women. Both declared themselves quite happy to publish anything that anyone is prepared to pay for, provided it is within the letter of the law—although *The Times* did admit to having had trouble over an advertisement for a Scottish lawyer when the intention had been to recruit a lawyer expert in Scottish law.

In the United States some newspapers have had to close their women's appointments column. Have British papers received any complaints? The *Daily Telegraph* says no, *The Times* says yes—a couple—but as the advertising manager said in another context, *The Times* is read by some of the best brains and the biggest cranks in the world.

On the subject of pay discrimination the Canadian High Commission said this week that its women scientists are paid the same as its men. At South Africa House they said that in industry women's pay is not always the same as that of men, but that in the Civil Service it is—"Well, there might be a few bob difference".

The president of the Women's Engineering Society, Miss Peggy Hodges, said that there is a large area in British industry where pay is nominally equal,

but where equal opportunity is quite another matter; women have to be better than men to hold down the same job, she said. What did she know of the position in America? She said that at the Third International Conference of Women Engineers and Scientists in Turin last September, she had the impression that in the United States also no more than lip service is paid to equal pay and that there certainly wasn't equal opportunity and she got the impression that "the position was, if anything, slightly worse". Oh dear. And when David Layzer, Randy Levine, Martha Schwink and company can spare a glance at their own problems and away from their suffering cousins 10,000 miles away in Sydney, perhaps they might read an article in *Science* (174, 270; 1971) which suggests that there might be a few battles over equal opportunity still to be fought on the good soil of the homeland before they venture so far abroad.

However, to keep their fighting pecker up with a sniff of victory, we did also ring the Australian Atomic Energy Adviser in London who placed the advertisement. Had anyone ever refused to carry one of his advertisements? no. Was there much in the way of protest about unequal pay in Australia? Well, quite a bit, he said. Could he foresee a time when women in Australia's Commonwealth Civil Service would be paid the same? Mr Fry said he wouldn't like to hazard a guess. In half an hour he rang back. Women scientists in the Australian Civil Service are to receive equal pay from January 1 next year. One more down, a few more to go.

TECHNOLOGY

A White-hot Haze

THAT the understanding and practice of technology must play a larger part in school timetables was the basic assumption behind a one day conference at the Open University last week on introducing technology into the school curriculum. It was also the only area of clear agreement.

The conference, sponsored by the Guinness Awards Scheme, was partly held to gauge reaction to a proposed conversion course in technology for teachers that Mr Geoffrey Holister, Professor of Technology at the Open University, hopes will be approved in principle by the university senate at its February meeting. The details of the course have yet to be worked out, but its aims are to provide teachers with an awareness of technology and its social implications, and an ability to solve problems put before them. It would also help teachers to pass on these abilities to their pupils.

What all this means in practice is far from clear—what people mean by tech-

nology varies considerably from applied science to a rather diffuse sort of sociology. The forty participants, from universities, colleges of education, the Schools Council and the research councils, also disagreed about whether technology should be taught for its own sake—with all the disciplines that embraces—or whether teachers in all subjects upon which technology impinges should be made more aware of technological implications and should then cooperate to encourage children to tackle suitable projects. This second view that technology should be taught by a change of attitude rather than a change of subject was the more popular at the conference and was clearly seen by some as part of a more broadly based approach to education as a whole, so that subjects that interrelate are taught together, in the humanities as well as the sciences.

The Open University's proposed course was cheered on, but if technology is to be introduced into schools by retraining teachers some of the participants were clearly apprehensive about the amounts of equipment that will be needed. Professor Holister suggested the provision of kits of the type to be used for the Open University technology course might help. But others argued that kits are limiting and tend to become an end in themselves as Professor Carter of Salford University claimed the Nuffield Science O- and A-level kits have become. Should technology in schools be the solving on paper of problems with as many social and economic aspects as technical ones, or should it be the understanding and use of computers and other technical equipment? Either way there were warnings that technology in schools will cost money. Those involved in A-level courses in engineering claim that a teacher cannot handle classes bigger than twelve if open ended problems are to be studied like the technical, social and economic problems of high rise flats.

At present technology in schools is encouraged largely by the Schools Council's Project Technology — which began life in 1967 and which provides teaching material to 1,000 schools. This material is soon to be published in book form. After Project Technology's demise in August 1972, there will be little active encouragement of school technology other than by a number of bodies that intend to carry on Project Technology's work, although, to date, they have more enthusiasm than money. There are also fourteen technology advisers to local education authorities and four (there are more planned) local science and technology centres which provide schools with facilities. But with 163 local education authorities in England and Wales alone, these are only

a drop in the ocean, unless something like teacher retraining is undertaken.

What emerged from the conference was a rather hazy conviction that more must be done to introduce technology into schools. But what that technology in fact is, and how it should be taught, have yet to be defined.

ANTI-VIVISECTION

Cells do not Suffer

THE Anti-vivisection Society's bandwagon rolls on with the release of a film last week to promote opposition to experiments on living animals and a campaign for a national centre to investigate methods of research without vivisection. When the society was formed in 1875, 300 experiments a year were carried out on live animals; last year the figure was just over 5½ million. The society opposes in principle all painful experiments on live animals even where man benefits directly, but appreciates that these cannot be stopped overnight. Its first object is therefore to change the law so that no animal may be subjected to vivisection if there are alternative methods—such as cell culture—available.

The society claims that support for its cause is growing. One hundred and thirty Members of Parliament are said to have pledged their support, and the society claims that a letter sent to the 14,000 researchers licensed by the Home Office to work on living animals produced 1,000 replies supporting in principle the research centre they propose. They also admit to receiving 1,000 letters against their proposal.

Asked to put a figure on the cost of such a centre, the society estimates that the first step in such a scheme—the collation of all known material on research methods other than vivisection—would cost £0.5 million, but that the actual cost of building the centre is anybody's guess.

Mr Richard Body, MP, one of the society's vice-presidents, claims that Britain is "far behind countries such as Turkey, Yugoslavia and even Russia" in concentrating on cell and tissue culture rather than vivisection, although in fact the legal controls in Britain are among the stiffest in the world. Every laboratory has to be licensed by the Home Office (there are about 600) before it can experiment on animals, and every researcher within a laboratory has to have a personal licence. Whether the anti-vivisectionists will ever command enough public and parliamentary opinion to achieve their aims remains to be seen, but the adoption of a resolution by the Consultative Assembly of the Council of Europe last January recommending a study of alternative methods to vivi-

section may lend some support to Mr Body's claim that the movement is "rapidly gaining ground".

EUROPEAN LABORATORY

Still Waiting

THE absence through ill health of Professor G. Puppi, chairman of the Esro council, from the council meeting held in Paris on November 23 and 24, caused the expected press conference to be cancelled and probably saved Esro a great deal of embarrassment. The Esro council continued its meeting this week and it is expected that an announcement about the future of the European Space Research Institute (Esrin) will be made today (December 10).

The meeting held two weeks ago was notable for the measure of disagreement among the delegates on the future course of Esro. In particular, no decision was reached on the vexed question of whether Esro is to continue supporting Esrin and the Italian plan for the future of the laboratory (see *Nature*, 234, 165; 1971) was not discussed—ostensibly because of the absence of Professor Puppi who has been personally conducting negotiations with the interested parties. In spite of there being no detailed discussion on the future of Esrin, the Italian delegation confirmed reports that they were determined to keep some Esro activity at Esrin—according to the plan that was discussed this week, the Italian delegation suggested that the Centro Nazionale delle Ricerche (CNR) contribute \$1.7 million towards the running costs of Esrin and Esro the remainder—which would amount to \$1.0 million.

The original objection to the continued existence of Esrin within the Esro framework was that it carried out research that was not compatible with the present aims of the organization. It was therefore surprising at the meeting on November 23 and 24 that both the German and Dutch delegations made statements to the effect that the continued support of Esrin in its present form amounted to a financial problem for the organization.

The threat of the Italian withdrawal from Esro hung over the meeting (see *Nature*, 234, 3; 1971) and although it was agreed at the Esro council meeting held in July that Germany, France, Italy and Britain would continue to support the applications satellite programme, the Italians now mentioned that they were reserving their support—probably until a decision was made on the future of Esrin. As a result of the Italian change of heart the Esro council this week reconsidered the future plan for Esro that was mapped out in July.

EDUCATION

Craft Training Examined

A MUCH needed inquiry into the relevance of school teaching in industrial training is to be undertaken in a four year research project at the Centre for Science Education, Chelsea College of Science and Technology. The project, financed by a grant of £45,580 provided jointly by the Engineering Industry Training Board and the Leverhulme Trust, is to be directed by Dr Erica Glynn, who also directed the one year feasibility study that led up to the formation of the present project.

One of the objectives is to see how the performance of industrial trainees depends on training at school. In particular there will be an attempt to relate the performance of trainees who have studied science by an innovative scheme—for example the Nuffield scheme—to those who have learnt their science in a

more conventional way. A further objective is to obtain information on what training best suits school leavers of differing educational backgrounds.

Perhaps the most important by-product of the inquiry will be to forge an association between school and industry and to correlate teaching methods and training. It is this aspect of the work that has attracted the support of the Engineering Industry Board, which hopes that the inquiry will lead to a more efficient and practical training scheme for industrial trainees.

The impetus for the new study comes not only from the one year feasibility study, but from a similar study of the training of craft apprentices started in 1966 at the Perkins Engines company which was also supported by the Engineering Industry Training Board. This report, published earlier this year, suggests that the choice of methods open to the craft instructors is considerably

wider than previously assumed and that "guided discovery learning" is particularly effective.

The study team plans to concentrate its investigations in selected areas where the project team and people in education and industry will cooperate to define the problems to be studied to minimize any misunderstanding.

The research programme will be in three phases:

- Local in-depth studies to develop tests and questionnaires.
- The testing of detailed hypotheses, making use of information obtained in the first stage of the investigation, by following the performance of potential trainees from their last year in school through their first year of training.
- Analysis and evaluation with continuing study of the performance of some craft trainees into their second year of training.

SCIENCE POLICY

Lord Rothschild Says It Again

THE Royal Society of Arts, more fully known as the Royal Society for the Encouragement of Arts, Manufactures and Commerce, heard from Lord Rothschild himself, on Wednesday this week, of the philosophy underlying his proposals for the reorganization of the British government's interests in civil research in Britain and in particular for the redefinition of the relationship between the research councils and government departments. Quite apart from the claim on public attention which his report (see *Nature*, 234, 169; 1971) has established, there is also a chance that Lord Rothschild will become the most amusing civil servant to work for the present government.

The classification of research attracted a good deal of his irony. He complained of those "ex-research workers who are the high priests of the cult" who have kept the "taxonomic bandwagon" rolling and in particular of the concept of "pure basic research". But what about research on the nature of the immaterial world? Is that impure? "One had better ask Zuckerman" for, as Lord Rothschild pointed out, Lord Zuckerman's co-author of the Gibbs-Zuckerman report in 1961 "is no longer with us". On that classification, there was also "objective basic research" which is relevant to known objectives in technology, applied project research with a practical goal, applied operational research which is the improvement of the devices which exist already, and development, to bridge the gap be-

tween research and production. "One wonders for whom this elaborate taxonomy was necessary and to whom it is useful."

The taxonomic point is important in Lord Rothschild's argument because it is the starting point for his principal conclusion and on Wednesday he complained of the taxonomy put forward by Sir Frederick Dainton's committee, with its concepts of basic research, strategic research and technical research. In practice, he said, it is not possible to make distinctions like these with any accuracy.

Basic research, however, does have a place in Lord Rothschild's scheme of things. Basic research "is done solely to increase knowledge". Researchers must be competent but need not justify their activities "on the grounds that they may help mankind". It may happen that basic research turns out to have practical value, but that is not essential. Society will back good people "provided what they want is not too obviously anti-social. Whether society will go on backing every Tom, Dick and Harry who is inquisitive but not too gifted, and let them do what they like at public expense for three or so years at a university after graduation, is a matter on which we would do well to ponder. We do not want to have too many lift attendants, taxi drivers or uniformed commissionaires with PhDs in the natural sciences . . .". The strength of Lord Rothschild's taxonomy is its simplicity—there are only two

categories, the second of which he calls applied research and development. "It is indistinguishable from pure research as regards how it is done. The distinction lies in why it is done and who wants it done." Applied research needs an objective—putting men on the Moon, providing blind people with artificial eyes, making cars less noisy and noxious, reducing collisions in the English Channel, providing three-dimensional colour television screens. Indeed, the choice of technical objectives is so great that, in Lord Rothschild's view, it is no longer true—if it has ever been true—that what "can be done will be done". On the contrary, "we have, in fact, got to the end of the road, where the man who determines the objective for which applied research is necessary has got to justify the objective to a form of shareholder, whether it be the electorate and their representatives in Parliament or that somewhat elusive and inarticulate person, the shareholder in a company."

In Lord Rothschild's view, outside scrutiny is also required for basic research projects. Some kind of basic research "might have dangerous consequences or side effects" and society could not be expected indiscriminately to acquiesce in the conduct of work like this and the dissemination of the results. ". . . Sooner or later we shall have to control those types of basic research whose indiscriminate exploitation would or might be harmful to society. Interference with the liberty

of the subject? Yes, but is there ever, in reality, absolute liberty? I think not."

Lord Rothschild is not, from what he said on Wednesday this week, an instinctive supporter of "big research". The proton accelerator being built near Chicago on 6,800 acres of prairie, and already equipped with three artificial lakes for fishermen, two herds of buffalo and an office in Chicago for the recruitment of black workers, had already cost £100 million and was no doubt a forerunner for an instrument that would cost ten or a hundred times as much. Such a "gadget . . . with or without the lakes and buffaloes" was outside the British purse, "but in our own modest way we have similar intentions". Lord Rothschild went on to refer to the proposal that the Science Research Council should finance a high flux beam reactor at a cost of £22 million and he wanted "the scientific establishment" to ask whether it might not be better to spend the money on Titian's *Death of Actaeon* (which would still leave room for another nine equally expensive paintings), twenty miles of motorway, four hospitals, 300 adventure playgrounds, four prisons, 200,000 television sets, two Jumbo jets or 4,500 houses.

How should people decide what projects in applied research should be supported? Quality of research and individual creativity are no less important than elsewhere but there are also questions to be asked of economists, those who value clean air and clean country and even those who worry about law and order. "These deep and fundamental national questions cannot be decided by scientists alone" and in this sense Britain shares with other nations an anachronism. He was not seeking a regime in which scientists would be told meticulously what to do but he did protest against the "pedestalization of science" and the way in which the admiration of the British for pure science spilled over into the making of decisions on applied science. "Have we not got 4.6 Nobel prizewinners per ten million of our people in comparison with America's 3.3?" Scientists might have a part to play in studying problems such as urban conglomeration, agricultural needs and drug addiction, just as do other people—sociologists, engineers, lawyers, economists, accountants, mathematicians and administrators. Unhappily, in Lord Rothschild's view, the government was still too wedded to the idea that in circumstances like this it was necessary only to find good scientists "and let them get on with the job". He blamed not so much the people themselves as their willingness to invoke the outmoded Haldane principle, with its justification of scientific freedom or, rather, *laissez faire*.

Lord Rothschild complained that one of the consequences of the Haldane principle had been to polarize society into scientists and the rest, with detrimental effects on government research and development and with the result that there had emerged autonomous bodies, the research councils, which were accountable to Parliament but "not accountable to anybody else in spite of their names which include such bizarre words as agricultural, medical and natural environment. Is it not strange that though the taxpayer pays for these bodies, he has no say in what they do?"

Lord Rothschild went on to say that "we scientists are neither black, selfish, thoughtless and unpatriotic; nor are we white, selfless, unthoughtful patriots. Like virtually everyone else, we are grey curates' eggs." And scientists are conservative and were hanging on to the Haldane principle, as interpreted, without recognizing how much damage it had done in polarizing society and the civil service.

What is to be done? Lord Rothschild was optimistic about the problems of the civil service, which will be solved "during the next five or so years". Nor is he worried about basic research, an activity in its own right even if it does consume between 13 and 17 per cent of the British government's expenditure on

research. But he did ask that applied research should be linked with practical objectives, that research workers should not be solely responsible for formulating these objectives nor even for deciding whether "the objective requires research for its achievement. He should not decide that the research should be done, assuming it is necessary. He should not decide when to stop. Nor should he decide to change the objective in midstream, however desirable it may seem to him to do so." Rather, it is for scientists to do the research and to help out when they can.

This is where the doctrine of the customer and the contractor comes in. Lord Rothschild has no strong opinion, to tell from his lecture on Wednesday, about the kinds of basic research that should be carried out. "What, however, I do object to is virtually all medical, agricultural and environmental research being controlled autonomously by scientists and to a lesser extent mathematicians and engineers, with concomitant downgrading of the research commissioned by government departments and, with a few exceptions such as Bell Telephone Laboratories, by industry. We must, I believe, oppose the deliberate creation and nurture of this kind of scientific elite—the autonomous haves and the departmental or industrial have-nots."

By his own admission, Lord Rothschild seems well aware that his philosophy "is anathema to very many scientists, particularly of course to some of those intimately connected with our research council system". Haldane has been beatified by the scientific establishment and Lord Rothschild was particularly scornful, in his address on Wednesday, of Sir Harold Himsworth's defence of the research council system in his book *The Development and Organisation of Scientific Knowledge* (Heinemann, 1970). Is it possible that scientists are so corrupt that they will cook the books when working for government departments? Can ministers in the 1970s actually suppress facts? Is it sensible to fear that venality in government departments can survive in the face of honesty from abroad?

But what is it all for? Lord Rothschild's complaint is that the scientific community is clinging to outdated concepts. He considers that there is no such thing as science policy but that it is important to develop policies on pollution, ocean resources, food supplies and so on. But "science as a whole is not an activity to be carried on in isolation. It must be part of society's integrated effort to make the world a better place." And it is for "democratic society itself and its elected representatives" to give scientists their marching orders.

Scientific Administrators

LORD ROTHSCHILD said this week that within five years there would be a free interchange of scientists and administrators within the civil service. The present reluctance to have such interchange is, according to Lord Rothschild, not due to administrative, financial or geographical difficulties but because a belief pervades the civil service that administrators cannot play an important role in scientific policy making and that scientists make bad administrators. The truth, according to Lord Rothschild, lies somewhere in between.

Mr William McCall, general secretary of the Institution of Professional Civil Servants, who has been agitating for such an interchange for some time, said this week that he was delighted with this aspect of Lord Rothschild's lecture. Mr McCall added that the foundations of a better arrangement for interchange will be laid soon and that he was determined that the system should be in full operation within five years.

NEW WORLD

NATIONAL SCIENCE FOUNDATION

Steuer Confirmed

by our Washington Correspondent

AFTER twenty minutes of gentle and rambling questioning of Dr H. Guyford Steuer last week, the Senate Committee on Labour and Public Welfare agreed, as everybody expected, that Dr Steuer is suitably qualified to be the next director of the National Science Foundation. The Senate later went through the formality of confirming his nomination, and Dr Steuer is now all set to take over from William D. McElroy who leaves the NSF in February next year to become chancellor of the University of California at San Diego.

Last week's gentle grilling—if a series of congratulations and a dialogue in which committee members had most of the say can be so described—elicited few surprises about Dr Steuer's policies for the NSF. Asked by Senator Edward M. Kennedy about his attitude to the RANN (Research Applied to National Needs) programme, for example, Dr Steuer replied that the programme "is a very important programme to the NSF" since it helps to turn out from the universities more students who are aware of society's problems and needs. The programme also happens to be one on which the NSF is particularly keen, in spite of congressional disfavour last year, and Dr Steuer's background as an engineer should help him in his arguments before Congress next year when he asks for more money for the RANN programme.

As for institutional support grants, which last year were severely reduced in the Administration's budget requests to Congress, reinstated by the authorizations committees but partially withheld by the Office of Management and Budget, Dr Steuer seemed to be in two minds. As a university president who has been particularly successful in getting NSF institutional support in the past, Dr Steuer considers such grants to be "very valuable", but the director-elect, perhaps toeing the Administration line, pointed out that when it comes to apportioning scarce resources, some areas are bound to suffer, the clear inference being that cutting institutional support may be less damaging than paring funds for particular areas of research—a drop in funds for high energy physics has already "contributed to unemployment", Dr Steuer said. Nevertheless, if Dr Steuer is put in the position of arguing for a cut in institutional support grants for the 1973 budget, somebody is bound to point to his testimony before the House Subcommittee on Science, Research and

Development in 1969, when he thoroughly endorsed institutional support as a particularly valuable instrument for stimulating basic research in the universities.



Dr H. Guyford Steuer, the next director of the National Science Foundation

That Dr Steuer would be acceptable to the Administration and to Congress has scarcely been in doubt since the National Science Board recommended his name to the White House nearly three months ago. His background as a scientist and engineer, administrator and veteran of the Washington science advisory network (see *Nature*, 234, 122; 1971) won him points with Congress and the White House was also impressed by the fact that he is a Republican who is unlikely to be at odds with the rest of the Administration on major policy issues. Dr Steuer's political background certainly ensured that there would be no repeat of the 1969 performance when Franklin Long of Cornell University had his nomination to the NSF with-

drawn by the White House because of his opposition to the ABM system.

ASTRONOMY

New Face for Arecibo

by our Washington Correspondent

A CONTRACT has at last been awarded for resurfacing the 1,000 foot radio antenna at Arecibo in Puerto Rico. The work, which will cost about \$3.76 million, will take about two and a half years to complete, and should improve considerably the sensitivity of the telescope—allowing detection of about twenty times more radio sources than the presently known 5,000—and enable it to be operated at wavelengths as short as 6 cm, compared with the present minimum operating wavelength of 50 cm.

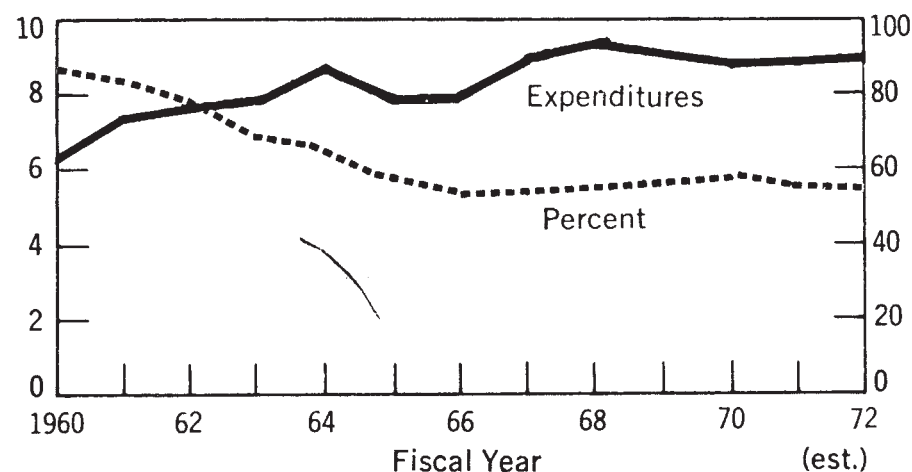
The chief objective of the work is to improve the accuracy of the surface of the telescope by replacing the present wire mesh with perforated aluminium panels—37,000 panels will cover the 18.5 acre surface of the antenna. To achieve the desired operating performance, the radius of the sphere must be accurate to within 3.2 mm at each point, compared to the present surface accuracy of about 1.5 cm, and the firm that has been awarded the contract, LTV Electro-systems Inc. of Dallas, Texas, estimates that the alterations will add some 100,000 pounds to the weight of the surface.

One of the terms of the contract is that the work should not be allowed to interrupt research with the telescope, and Mr Robert Matyas, Director of the Department of Construction at Cornell University, who is in charge of the operations, said last week that he is confident that any undue disturbance can be avoided since the resurfacing would be carried out on one area at a time.

Federal Research and Development Expenditures

(Billions of dollars)

(Percent of R & D total)



ETHICS

Another Commission

by our Washington Correspondent

THE standard way to deal with any vexed problem is to appoint a committee to chew over the issue in the hope that it will come up with a workable solution. The social, ethical and legal implications of advances in biochemical research are, it seems, no exceptions to this general rule, for the Senate last week agreed to appoint a full-scale commission to take a hard look at the ethical problems associated with organ transplants, abortion, prenatal diagnosis of genetic defects, genetic engineering and a host of other problems now troubling some members of the medical and scientific community. If the commission does see the light of day—compamion legislation is bogged down in committee in the House of Representatives—it will rightly be based on the assumption that such issues transcend the expertise of health scientists and, as the Senate Committee on Labor and Public Welfare says in its report on the legislation, “We can no longer ask them to grapple with these issues alone”.

The legislation designed to set up the commission was reported out of the Labor and Public Health Committee early last week, and approved by the Senate with little discussion four days later. It calls for the setting up of a fifteen-member commission appointed by the President from the fields of medicine, law, theology, biological science, social science, philosophy, humanities, health administration, government and public affairs. It is intended that the commission would deliberate for two years, at the end of which it would submit a report to Congress and the President of its findings and recommendations.

Among the duties with which the commission will be charged are to analyse and evaluate “scientific and technological advances in the biological sciences, past, current and projected, and then to assess the implications of such advances for individuals and for society”. An equally important part of the commission’s work would be to analyse public understanding of such issues through the use of seminars and public hearings, and to evaluate public attitudes to biomedical research. The legislation authorizes an expenditure of up to \$1 million for each of the two years for the commission to perform this Herculean task.

One day of hearings on the legislation, held early in November, elicited considerable support for the idea from members of the biomedical community, although almost without exception, the witnesses drew attention to the complexity of the task facing such a com-

mission. Dr Abram Chayes of Harvard Law School, for example, suggested that the commission is needed because it would have the time and resources that have been missing from previous attempts to view the problems, and Dr John Najarian of the University of Minnesota said that the commission would do valuable work if it came up with guidelines on, for example, what is considered to be a definition of death.

A note of warning was, however, sounded by reports and testimony from members of government agencies. Dr DuVal, Assistant Secretary for Health and Scientific Affairs of the Department of Health, Education and Welfare, said, for example, that “the issues are so complex and the underlying currents of change moving so swiftly that in our view no attempt to describe this particular healthscape, at what would have to be a given moment of time, could be definitive for long”. But the committee does not agree, for it is looking to the commission to recommend procedures to grapple with the important problems on a continuing basis. Perhaps the most valuable accomplishment of such a commission, however, would be to open up to public discussion important ethical and social issues that have in the past been unnecessarily private.

PREDATOR CONTROL

How to Kill Coyotes

by our Washington Correspondent

LAST year, 74,000 coyotes were killed as a result of federally financed poisoning programmes, which have been under

the control of the Department of Agriculture for the past 40 years. But, according to Senator Gale W. McGee, there has never been a census taken of the number of coyotes in the United States, and “while it appears we have been attacking the problem with vigour and persistence, we have not made any attempt whatsoever to determine and define the scope of the problem itself”. This and other aspects of predator control in the United States will, however, be the subject of an inquiry next week by Senator McGee’s Agriculture Environmental and Consumer Protection Subcommittee of the Senate Appropriations Committee.

For many years, it has been the practice of predator control programmes to kill predators whenever and wherever they appear, with poisoning usually the first line of attack. The effects of such policies on non-target species are too numerous to mention, but of particular concern are episodes such as the killing of several dozen eagles in Wyoming earlier this year during an unauthorized control programme.

Another aspect of the problem which Senator McGee hopes to look at during his hearings is the scope of the damage that is done each year to livestock by predators. The Department of Agriculture, for example, estimates that in 1970 predators accounted for the loss of some 130,000 sheep in Wyoming, but it is not clear how that estimate was derived. Without at least any attempt to determine the scope of the problem, no realistic policies can be formulated, and the Department of Agriculture will clearly have to defend its frontier tactics of simply killing everything in sight without taking stock of the situation.

Short Notes**DDT in the Oceans**

NEARLY 20 million tons of DDT have been manufactured in the world since 1944, of which as much as 25 per cent may have been transferred to the sea. About 0.1 per cent of all the DDT ever produced, or 20,000 tons, resides in the marine biota. So estimates a panel of the National Research Council in a report published last month (*Chlorinated Hydrocarbons in the Marine Environment*. Panel on Monitoring Persistent Pesticides in the Marine Environment. NRC, Washington, 44 pp.).

Research on Research

NOT merely is it possible to sponsor research on transportation but, as the Science Council of Canada has shown in its Special Study No. 17, now published, it is possible to sponsor research on research on transportation. The first volume, mercifully short, of this

three-volume study, says that twenty man-months of professional effort “cannot pretend to have done more than scratch the surface”. Even so, the document does play a good deal with numbers, pointing out that research on transportation, equipment as well as distance, amounts to only \$40 million a year, rather less than 0.5 per cent of total expenditure on transportation as such. Worse still, most professional effort goes on such things as air transport. The document pleads that there should be a fuller appreciation of the need for a systems approach in the study, the design and the operation of transport systems—that industry should be regarded as part of the system of research, that there should be less chauvinism and more international collaboration on good works such as the development of new methods of transport.

NEWS AND VIEWS

Politics as Applied Mathematics

THERE is very little chance that politics, variously known as the art of the possible and the art of the impossible, will become an entirely rational process, but it is important not merely for politicians and mathematicians but for ordinary electors that a great deal has been done to formulate in mathematical language some of the problems with which politicians are concerned. In the past year or so, mathematical models have been constructed for such things as the economic systems of nation states, the relationship between industrial activity and environmental pollution and the operation of hospital services.

Each of these devices is, potentially at least, of considerable importance to politicians and public administrators. Predicting what will happen to the level of unemployment from an increase of income tax can be a much more precise procedure than anybody would have guessed in the days when macroeconomics and differential equations were both considered by the world at large to be secret mysteries. It is sometimes hard to tell from the way in which governments actually behave, and from the air of injured innocence with which they greet predictable consequences of actions taken deliberately but blindly, that the lesson has been absorbed that much of the working of systems even as complicated as social systems is capable of objective analysis, but there has been some progress in this direction.

It may not be surprising that the most useful work has been done in defence, arms control and disarmament, for these are fields in which mathematicians have long been involved with those who are paid for making subjective judgments about imponderable issues. The article by Dr Ian Bellany on page 361 of this issue of *Nature* is yet another illustration of the way in which it is possible to describe mathematically what may be done to throw light on conflicts such as those which exist when opposing nations are asked to make reductions of military forces.

Dr Bellany's conclusions, are unlikely to bring the SALT talks to an immediate end when they are resumed in the new year, but they should help to show how straightforward can be some of the conclusions drawn by mathematicians about military situations. The starting point for Dr Bellany's argument is the assumption that the two sides are to begin with in a state of military balance which can be expressed by the numerical equality of two mathematical functions, each representing the way in which the military strength of each side is determined by parameters such as the size of its standing army, the number of tanks which it possesses and so on.

The argument is chiefly concerned with conventional weapons and with the possibility that there might in the next few years be a serious attempt to bring a balanced reduction of military forces in Central Europe. If the state of balance has been achieved because both sides have reached the point at which they have ceased to invest in new armaments, but are instead content merely to keep their armies up to strength and to replace equipment as it wears out, elementary calculus is enough to show that in any programme for disarmament there should be equal proportional reductions of arms on both

sides. The point is important because its validity does not depend on the different ways in which the military strengths of the two sides may be differently determined by armaments of different kinds.

But if each side agrees, for example, to reduce its number of troops and of tanks to go with them by, say, 25 per cent, is there a danger that the outbreak of hostilities would then give one side a better chance of winning by causing damage to its opponent? Simply because defensive positions are frequently safer than offensive postures, it turns out that further conditions must be satisfied by the proportionate reduction of force. Problems like these, in the past few years, have been tackled successfully by means of geometrical multivariate models. This, for example, is the way in which it was shown in the 1950s that a balance of mutual deterrence with ballistic missiles is possible if and only if both sides have more than a certain minimum force—if one side has too few missiles, it can always legitimately fear that these will be destroyed by a pre-emptive strike by the other side, which would then be free to go on and hold the defeated country to ransom. The same argument has more recently been used to demonstrate that multiple independent re-entry vehicles would upset the strategic balance between the United States and the Soviet Union which has been expensively established during the past decade.

By now, there is a distinguished if small body of literature on these and related problems. The late Professor Lewis F. Richardson was one of the most stimulating of contributors, with books such as *Statistics of Deadly Quarrels* (Chicago, 1960). Richardson's chief contribution was to show that differential equations can in many circumstances accurately describe the ways in which an arms race between two close opponents may on some occasions be stable and on some occasions be unstable—in retrospect, for example, it is clear that the principal opponents in the First World War can be accurately described by Richardson's equations. But there are other problems to be considered, notably the economic constraints which increasingly determine the scale on which military forces can be developed in modern states and W. R. Caspary has made distinguished contributions to those aspects of these problems.

In the 1960s, the games theoreticians entered the scene and, in spite of the way in which the name of their craft seems continually to bring them into disrepute among ordinary people (not to mention politicians), nobody will deny that their influence has been stimulating and beneficial. The much maligned Mr Herman Kahn, once described as the "Herman Kahn of strategy", has helped enormously to demonstrate the intellectual interest and importance of mathematical models in military and political conflicts. Politicians who think otherwise should reflect on the value of abstract discussions of how to behave in the game of chicken—that teenage sport in which young people drive headlong towards each other to see which driver loses his nerve first—an unpleasantness for the loser—or whether neither loses his nerve—a greater unpleasantness for both.

PROTEINS

Sighting the Sites

from our Molecular Biology Correspondent
A STRONG contender for this year's *concours d'élégance* of protein chemistry is to be found coyly nestling in the yellow pages of the current issue of the *Biochemical Journal*. This is an article by Green, Konieczny, Toms and Valentine (125, 781; 1971), and though it is overtly about the binding of biotin to avidin, both the principles and the results are of much wider relevance.

The background is as follows: avidin is a protein made up of four identical chains, of some 15,000 molecular weight. Each of these has one binding site for biotin, with which it combines with enormous avidity. The only part of the biotin molecule indispensable for binding is the ureido ring. By analogy with what is known about the binding of ligands to enzymes, it might be supposed that the binding site would be situated in a cleft or pit in the surface of the protein. It should be possible, Green and his colleagues reasoned, to find out something about the nature of this cleft, and also about the disposition of the subunits in the tetramer by looking at the interaction of avidin with bifunctional ligands.

Green *et al.* therefore synthesized a series of bisbiotin derivatives, in which the rings were joined by hydrocarbon chains of different lengths, such that the number of bonds between the biotin carboxyl groups varied between nine and twenty-five. Below some critical chain length it would be supposed that the separation of the biotins would be too short to reach between binding sites on two protein molecules if these extend well below the surface, and indeed it was found that when the number of bonds was anything less than twelve, the bifunctional reagent was able to react with only a monofunctional stoichiometry, and no associated forms of the protein could be detected. At twelve, bifunctional behaviour set in, as judged by the combining ratios and also by the appearance of polymers in the electron microscope. These polymers took the form of linear chains of width corresponding to that of single avidin molecules. The shape of the ligand titration curves (determined by displacement of a dye from the binding site), as well as the ease with which the aggregates could be depolymerized by addition of an excess of ligand, indicated, however, that these chain lengths were barely sufficient for stable cross-linking. The polymers showed few branch points, and being linear, evidently consisted of protein molecules joined by way of two bifunctional ligands to either neighbour. A periodicity corresponding to the width of the avidin tetramer was clearly visible. When the

chain length was increased above four-teen bonds, the polymers became more stable, and clear daylight could be discerned between successive units. At very high ligand chain lengths, the polymers became much shorter, betokening the formation of intramolecular links by the bisbiotin compound.

From these results much of interest can be deduced. The minimum length between the biotin carboxyls that will enable both ends to seat in the active site cavity is 15 Å. Above 17.5 Å the binding strength at both ends becomes comparable with that of the monofunctional ligand. It may thus be deduced that the carboxyl group at the extremity of the ligand locates some 9 Å below the surface of the protein. Moreover it follows from the progressive increase in periodicity of the polymer with ligand chain length, and also of the binding constant within the critical range of chain lengths, that the surface is in some degree compressible. The compression is evidently energetically expensive, and becomes exorbitant below a chain length of twelve bonds. (In long chains, the hydrocarbon, judged by the periodicity, is by no means extended, but obviously increases the thickness of the layers between the protein units.) The length of hydrocarbon at which intramolecular cross-linking sets in also gives a limiting measure of the separation of the binding sites on two subunits within an avidin tetramer. Taking 9 Å as the depth of the carboxyl group, it turns out that the sites must be separated by only 6–10 Å on the surfaces of the subunits. This, of course, could be increased if there were any kind of depression or channel between the sites, to a maximum of about 25 Å.

Contemplation of the possible arrangements of equivalent subunits within a tetramer reveals that they may be related by two-fold or four-fold symmetry (isologous or heterologous association). Only the former can lead to linear polymers, one molecule thick. The four-fold arrangements can lead to two-dimensional networks, or to a unidimensionally repeating system, in which, however, each molecule is associated in zigzag manner to two others. Thus although the subunits are too small to be resolved within the tetramer by electron microscopy, the electron microscope nevertheless discriminates between the possibilities, and establishes the symmetry relation between the subunits, showing them to be arranged in two pairs, tail-to-tail, with a two-fold axis down the middle, and a screw axis relating successive repeating units in the chain. The known accessibility of the bound biotin to biotin-requiring enzymes suggests that it lies in a rather broad cleft, partly exposed, very much like inhibitors in enzymes of known structure.

A fashionable protein, the subunit structure of which confers on it its characteristic biological properties, is concanavalin. The crystal structure is being hotly pursued in two laboratories, and Becker, Reeke and Edelman (*J. Biol. Chem.*, **246**, 6123; 1971) have now deduced from an electron density map of a complex of concanavalin with heavy atom containing ligands the disposition of the saccharide binding sites—arguably the most interesting feature that is to be had from the structure. There are four subunits, each of which possesses one saccharide binding site. The 2.8 Å electron density map shows that

Lead Ions in the Atmosphere

THE topical subject of cluster ions is aired in next Monday's *Nature Physical Science*, where Castleman and Tang of the Atmospheric Chemistry Research Group at Brookhaven National Laboratory describe the clustering of water molecules on ions of lead. The possible role of ion clusters in the upper atmosphere is receiving increasing attention, so that the laboratory demonstration by Castleman and Tang of the existence of clusters involving lead may soon find an application in theoretical studies on the transport of lead, both radioactive and stable, in the atmosphere. Their data may also account for the low mobility of radioactive lead ions in humid atmospheres.

Briefly, Castleman and Tang passed an ion beam consisting of Pb^+ through a reaction cell in which the concentration of water vapour could be altered, and the products were examined by mass spectrometry. Ions of the form

$Pb^+(H_2O)_n$, where n can be as high as seven, were detected. Castleman and Tang find three peaks in the mass spectrometric output for each cluster, corresponding to the major lead isotopes of mass 206, 207 and 208, and the peak corresponding to mass 204 can also be detected.

As well as demonstrating that clustering on lead ions can occur, the experiment has given some of the parameters of the reactions involved. From these data Castleman and Tang are already able to draw some conclusions relevant to the behaviour of lead in the atmosphere. For example, they say that lead ions in the troposphere resulting from the decay of radon will initially exist as clusters, and the species $Pb^+(H_2O)_6$ should be the most abundant. Such cluster ions will be removed by interaction with aerosols or by recombination with negative ions in the atmosphere.

the sites lie in cavities near the subunit interfaces. The tetramer is made up of two roughly ellipsoidal dimers at right angles, and the sites on different dimers are separated by 25 and 35 Å. Depending on the orientation of the sugar groups, which cannot be discerned at this resolution, two bound saccharides on one tetramer could be up to 47 Å apart—a rather small but feasible distance for the approach of agglutinating cell surfaces.

HUMAN EVOLUTION

Darwin Centenary

ON October 28–30, Rome was the setting for another celebration of the centenary of the publication of the *Descent of Man* by Charles Darwin (see last week's issue: 234, 251; 1971). The occasion was marked by a distinguished gathering of international scientists at the Palazzo Farnesina, home of the Accademia Nazionale dei Lincei. The Lincei is one of the oldest European scientific societies whose membership encompasses the broad sweep of natural philosophy in its true sense; no more suitable venue could be envisaged for a meeting that ranged so widely.

After a welcome by the President of the Lincei, Professor Beniamino Segre, and an introduction by Professor C. Barigozzi, the first session was addressed by Professor T. Dobzhansky (Rockefeller University) and Professor E. Mayr (Harvard University). Professor Dobzhansky, in a wide and deep analysis, emphasized the relative lack of differences between man and apes that are being shown by recent work in comparative biochemistry, but he also drew attention to the overriding distinctiveness of human culture in terms of symbolism, language, self awareness and death awareness. Plasticity of non-genetically determined behaviour was seen as a better adaptive strategy than fixity of behaviour in genes. Man, he insisted, is not a chance animal and natural selection is not a chance process but a feedback servo-mechanism between the gene pool and the environment. If variability is present between forms, natural selection must occur and innovative genotypes will be directional and lead to a closer fit with the environment. Evolution was seen as a synthesis of determinism and chance, a synthesis that is in itself creative.

Professor Mayr drew attention to the fact that much of the *Descent of Man* was concerned with sexual selection, and that this was rejected as an evolutionary process by many of Darwin's critics; he supported sexual selection by showing that it can confer reproductive advantage and lead to sexual dimorphism. On the other hand Professor Mayr could not agree that sexual selection has played an impor-

tant part in the development of human races but accepted that it may account for the acceleration of the process.

The afternoon of the first day was the turn of the "fossil men". Professor P. V. Tobias (University of Witwatersrand) gave a historical résumé of the evolution of the genus *Homo* in which he supported Darwin's prediction of Africa as the cradle of mankind, and took the opportunity of announcing the find of a new australopithecine skull in the breccia at Sterkfontein. In almost direct contradiction Professor G. H. R. von Koenigswald (Senckenberg Museum, Frankfurt) reviewed the oldest hominid fossils from the Far East and, after denying the hominid status of *Kenyanthropus wickerii*, postulated an Indian centre of dispersal of the early hominids in two directions towards Africa and Java. This viewpoint was succinctly countered by Professor Tobias, in discussion, by the remark that palaeontologists must work with the fossils that they have and not those that are not yet to be found!

In the same session Dr M. H. Day (Middlesex Hospital Medical School, London) reviewed the early evolution of *Homo sapiens* in the light of the recent

finds from the Omo Valley in Ethiopia. He emphasized the spectrum of forms that are emerging from the fossil record and contended that the mosaic process is becoming more and more apparent in this phase of human evolution. On the one hand, the *erectus*-like sapients such as Vértesszőllős, Omo II, Solo and Rhodesian form a "pithecanthropoid intermediate" group and on the other hand there is a group which includes Swanscombe, Steinheim, Skhul and Amud that could remain as "neanderthaloid intermediates".

The second day was the turn of the geneticists and behavioural scientists and included Dr G. A. Harrison (University of Oxford), Dr K. K. Kidd (University of California), Dr J. H. Crook (University of Bristol) and Professor L. Balout (Paris). Dr Harrison emphasized the influence of population genetics on evolutionary thinking and Professor Balout outlined the unity and continuity of stone tool cultures by breaking down a number of the artificial barriers that have been placed between cultural stages.

The final day included sessions on art and communication as well as the relationship between evolution and

More Ribosome Binding Sites Sequenced

THE three sites at which ribosomes bind when they initiate the translation of the three cistrons of bacteriophage R17 RNA and the binding site for the phage Q β coat protein cistron were sequenced in 1969 by Steitz and by Hindley and Staples. In next week's *Nature New Biology*, Staples and Hindley and Staples, Hindley, Billeter and Weissmann report the base sequences of the two other Q β ribosome binding sites, those of the Q β replicase and the Q β assembly protein. But although the sequence of six initiation sites in two messenger RNAs is now known, it is not possible to formulate a clear picture of how a ribosome recognizes an AUG codon at the beginning of a genetic message and correctly initiates translation.

There are two obvious ways in which, in theory at least, a ribosome might be able to differentiate between an AUG codon acting as an initiator and specifying formyl-methionine and an AUG codon internal in a genetic message which specifies methionine. One is that the initiator AUG codon might be in a region of the messenger with a specific and recognizable secondary structure; the other is that the initiator AUG codon might be preceded by some particular sequence of bases which the ribosome can recognize. The six initiation sites so far analysed do not, however, indicate any common secondary structure, neither do they reveal a common

base sequence which might signal initiation. All that can be said for the moment is that the sequence immediately preceding an initiator AUG is rich in purines. In short, there must be some molecular basis for the specificity of chain initiation, but, as Staples and Hindley say, "Knowledge of the six initiation sequences of Q β and R17 does not define the reason for this specificity".

Also in next week's *Nature New Biology*, Kozak and Nathans make the intriguing suggestion that the so-called assembly (on maturation) proteins of the RNA phages may act as regulators of translation of the phage cistrons. They report a series of experiments which indicate that on infection the bacteriophage RNA enters an *Escherichia coli* still associated with assembly protein. They postulate that either the assembly protein plays some part in "threading" the phage RNA through an F-pilus or, once in the cell, it may block the translation of all but the replicase cistron, such that at early times replicase rather than coat or assembly proteins are made. There is, of course, a precedent for this suggestion; late in infection phage coat protein blocks the translation of the replicase cistron. This effect of coat protein can be detected *in vitro* and no doubt Kozak and Nathans are currently trying to test with cell free systems their notion that assembly protein blocks the translation of the coat protein cistron.

theology. Interest in evolution remains high in both popular and scientific circles, and the Linnei was shrewd to catch the mood of the times by attracting a broadly based group of speakers each of whom had something important to contribute towards a better understanding of man's evolutionary history.

CLIMATE

Advance of Sahara

MUCH of the blame for the advance of the northern Sahara has traditionally been laid at the door of man, whose crude farming techniques have, since Roman times at least, created erosion and desert conditions in once fertile regions. A report by the World Meteorological Organization has now placed this belief on a scientific footing and it provides quantitative data on the importance of man's activities to the fertility of the region (H. Flohn and M. Ketata, *WMO Technical Note* 116, WMO, Geneva, 1971).

In addition to the detrimental effect of man, natural climatic changes also produce fluctuations in desert margins. In the Sahara it seems that the overall trend during the past 7,000 years is for the desert to dry up and expand (see, for example, J. L. Cloudsley-Thompson, *Internat. J. Envir. Studies*, **2**, 35; 1971), but this is not to say that farming activity is not important in the short term. During periods of delicate balance between the needs of vegetation and rainfall, overgrazing and the utilization of firewood can have a disastrous and irreversible effect.

The use of artesian wells and the intensive farming of date palms have a dramatic effect on the water balance. Since 1881 the number of date palms in the border region of the Tunisian Sahara has increased by more than 50 per cent. Flohn and Ketata estimate that the effect of this increase has been to reduce the level of subterranean water at a rate of 5 cm per year. Over a period of less than 100 years, it seems likely that effects of this magnitude will dominate over the long term natural climatic variations. As well as the direct effect on evapotranspiration of the economic importance of the palm, other farming techniques encourage the growth of the desert; notably, overgrazing and compacting of the soil by domestic animals such as the goat cause erosion. Even now, however, it may not be too late to take steps to rectify the situation, at least partially. At one farm site north of Nefta, an area of 50 hectares has been protected by barbed wire for the past 60 years. Here, the original vegetation has apparently been restored, with an average soil coverage of more than 80 per cent, a figure which contrasts

dramatically with 5 per cent coverage by the degraded vegetation on the other side of the fence.

The report concludes that the historically observed progress of desertic conditions towards the north is caused "not by a natural fluctuation in climatic conditions, but by human interference". Clearly, all activities involving the delicate water balance in the intermediate zone between desert and cultivated land should be carefully planned and coordinated to avoid further adverse effects on the water budget. In particular, caution over the extended use of artesian water and irrigation, encouragement of dry farming (such as olive farming), reafforestation and increase of animal husbandry to allow the return of natural vegetation could do much to redress the balance.

HAEMATOLOGY

Sickle Cell and Flight

from a Correspondent

IT has been known for about twenty years that aircraft flights can cause illness among people with sickle cell disorders—a hereditary disorder of the

blood that affects negro populations. But many negroes have only mild forms of the disease and are unaware that they are sufferers. To what extent are these people at risk when they embark on an aircraft flight?

Recent work on this question has been published in the *British Medical Journal* (**4**, 593; 1971) by R. L. Green, R. G. Huntsman and G. R. Serjeant, who suggest that all negroes should be screened for sickle cell disorder before flying. The problem arises because even modern jet aircraft are not fully pressurized as compared with ground level—the cabin pressure in a Boeing 707 at cruising altitude corresponds to an altitude of 5,000 to 7,000 feet—and many scheduled African flights still use unpressurized aircraft.

Sickle cell disease is an abnormality of the haemoglobin molecule. Several forms have been described; for example, substitution on the peptide chain of valine for glutamic acid results in production of haemoglobin S instead of the normal form, haemoglobin A, and another form which Green *et al.* found to be relevant to their studies is haemoglobin C. The abnormal haemoglobin renders the shape of the red blood corpuscles less stable and under conditions of low oxygen tension the

Reading through a UGA Terminator

THE closely related group of RNA phages which include R17, MS2 and f2 possess genomes which specify only three proteins, namely coat and assembly proteins, which form part of the viral capsid, and a subunit of the viral replicase. The phage Q β , which is not in the same serological subgroup as R17 and its relatives, specifies coat and assembly proteins and a replicase subunit but, in addition, a fourth protein known as A₁ or IIb, which weighs 36–38,000 daltons, can be recovered from Q β phage particles.

What is the nature of this fourth protein? According to the experiments of Weiner and Weber and of Moore *et al.* reported in next Wednesday's *Nature New Biology*, it is a larger than life coat protein made when ribosomes fail to terminate synthesis at the end of the coat protein cistron and continue to translate the intercistronic divide and part of the next cistron, which specifies a subunit of the replicase.

Moore *et al.* have shown that the first five amino-acids of A₁ are the same as coat protein and Weiner and Weber have shown that the first eight amino-acids of A₁ (or IIb) are the same as the coat protein. Furthermore, Weiner and Weber report that A₁ contains tryptophan, histidine and methionine, amino-acids not in the Q β coat protein, and that A₁ is never synthesized by mutant

Q β phage with an amber mutation in their coat protein cistron.

These data indicate that A₁ is probably produced when ribosomes read through the termination signal at the end of the Q β coat protein cistron. Because amber (UAG) and ochre (UAA) codons are efficient terminators unlikely to allow read-through, both groups argue that the terminator codon at the end of the Q β coat cistron is probably a solitary UGA codon, for UGA codons are known to be leaky terminators. Horiuchi *et al.* (*Virology*, **45**, 429; 1971) have also recently reached this conclusion and Weiner and Weber report experiments with a UGA suppressor strain of *Escherichia coli* which confirm it. They find that the molar fraction of A₁ (IIb) protein in Q β phage particles increases from 2 per cent to 7 per cent when the phage are grown on a UGA suppressor strain of *E. coli*. Furthermore, introduction of a streptomycin resistance mutation, which reduces the leakiness of UGA termination, reduces by about 30 per cent the yield of A₁.

The A₁ protein is about 2.5 times the size of coat protein, which means it has about 200 amino-acids in excess, and yet it can apparently become incorporated into the phage particles. It will be interesting to learn how this is achieved and how much of the replicase subunit sequence is found in the A₁ chain.

corpuscles—normally biconcave disks—are distorted into sickle-shaped cells. These cells clump together and block the lumen of the smallest blood vessels, impeding the flow of blood. The reduced oxygen supply leads to necrosis of the tissue, which most commonly occurs in the small vessels of the spleen where it causes severe abdominal pain.

Green *et al.* describe seven patients who suffered sickling crises during flight—one of whom was only a carrier of the disease but flew in an unpresurized aircraft at high altitude. The others were all homozygous for the disorder, but three of them aged between 22 and 48 had suffered no previous symptoms and were unaware that they had the disease. One interesting case involved a 15-year-old Jamaican girl known to have sickle cell disease of the haemoglobin C variety who first encountered the symptoms during a flight to Mexico City. Her symptoms persisted for five days until she moved to sea level at Acapulco.

Oddly enough, negroes with severe sickle cell anaemia may have fewer problems in flying than those with mild forms. This possibility arises because sufferers from the severe form of the disease have had so many similar episodes arising from minor provocations—such as respiratory infections—during childhood that much of the spleen has already been infarcted. This means that the flow through the small vessels of the spleen has already been largely cut out. A further factor in such patients is that they are anaemic from the constant destruction of red blood corpuscles by sickling so that their blood flow is less viscous and less likely to

become blocked. The most severe effects during flight are seen in those sufferers with haemoglobin C who are normally asymptomatic and not anaemic, and whose blood is of comparatively high viscosity.

Should there therefore be a revision of the 1961 recommendations of the Aerospace Medical Association which say that travellers with severe sickle cell anaemia or with haemoglobin C should not fly? In one sense these recommendations seem draconian in that sufferers from severe sickle cell disease may face little risk, and the recommendations may be an unnecessary obstacle to these negro travellers. In view of the findings of Green *et al.*, however, the recommendation with respect to haemoglobin C seems fully justified.

The problem is that of ensuring that travellers do not have the asymptomatic form of the disease. Hospitals already carry out screening procedures on patients of negro origin who are to be given anaesthetics, for severe sickling can occur if the oxygen tension is

allowed to fall under anaesthesia. When the possibility of sickling is anticipated, it can be prevented by giving high oxygen concentrations and intravenous sodium bicarbonate. The screening technique involves the microscopic examination of blood films under reduced oxygen pressure. If the characteristic sickling is seen, the exact type of disorder can be determined by electrophoresis. It may be that all prospective negro travellers should be screened in this way—certainly screening is essential for all aircrews.

CELL TRANSFORMATION

Surfaces Involved

from our Cell Biology Correspondent
TUMOUR virologists are, of course, always on the lookout for new parameters which they can measure and thereby decide whether a cell is transformed or untransformed. The classical parameter, the continued division of transformed cells in environments which severely restrict or totally inhibit the

Distinguishing Atlantic Cherts

ONE of the many unexpected results to emerge from the JOIDES Deep Sea Drilling Project has been the discovery of cherts in drill cores over a wide area of the north Atlantic. But what exactly are cherts? In general terms they are highly siliceous rocks comprising microcrystalline quartz and/or chalcedony—the chalcedony serving to distinguish them from other forms of sedimentary silica. On the other hand, Rex (in *Initial Reports Deep Sea Drilling Project*, Vols. 1 and 2; 1969 and 1970), in his preliminary report of Legs 1 and 2 of the JOIDES Project, included within the term chert rocks composed of cristobalite, a rather different form of SiO_2 . Thus although there is no doubt about the general definition of chert, the overall term covers differences in petrological detail.

Definitions as such are perhaps not too important except in so far as differences in petrological detail may conceal significant differences in origin. The upper Jurassic to middle Miocene cherts discovered in the Atlantic during Legs 1 and 2 of the JOIDES Project, for example, are widespread and occur in a wide variety of sediments including radiolarian oozes, nannoplanktonic chalks, zeolitic clays and foraminiferal silts. For these reasons alone, therefore, they are clearly important; and petrological differences are likely to imply differences in formation which could be significant. The recognition of such differences is thus critical, not least because the cherts have sometimes been correlated with seismic horizon A.

In next Monday's *Nature Physical Science* Calvert reports further on this theme. He confirms that the two forms of chert are clearly in evidence in the Atlantic but prefers to limit the term chert to the quartz-containing variety. The true cherts are thus the pre-upper Cretaceous samples whereas the younger "cherts" are, on the evidence of X-ray diffraction and infrared absorption data presented by Calvert, composed largely of disordered α -cristobalite.

It further emerges that the infrared absorption and X-ray diffraction spectra from the north Atlantic "cherts" are identical with those reported from siliceous concretions in Tertiary volcanic sequences, porcelanites from the Miocene Monterey Formation and certain common opals. In short, such silica structures are quite common in younger geological formations, are distinguishable from true cherts and, in Calvert's view, are better referred to as porcelanites. The origin of these porcelanites is not yet clear, however.

The classic definition of chert includes the possibilities of both organic and precipitate origin—and this may be relevant here too. For example, Ernst and Calvert (*Amer. J. Sci.*, **267A**, 114; 1969) regard the Monterey porcelanites as "an intermediate phase in the diagenetic modification of biogenous silica (diatomite) to chert, a phase which is not preserved in older (pre-Cenozoic) formations". The north Atlantic porcelanites may be similar; but they could equally well be alteration products of volcanic debris.

AQUATIC BIOLOGY

New Unit

A NEW Unit of Aquatic Pathobiology has been established at the University of Stirling with the help of a grant of £76,000 from the Nuffield Foundation. The director will be Dr R. J. Roberts, who is at present at the University of Glasgow. The university has on its campus a twenty-four-acre loch, an aquarium, and is close to the Forth estuary, so that the unit will be ideally situated for research on fish pathology, a field in which there is at present a need for far more research, particularly in connexion with the growing industry of fish culture. There is also a shortage of veterinary and scientific staff qualified in the field, and in this regard the new unit will have a programme of teaching at both the undergraduate and postgraduate level.

multiplication of untransformed cells, has proved and still proves to be enormously useful but tumour virologists are increasingly exploiting additional biochemical parameters.

Rubin and his colleagues, for example, have recently established that chick cells transformed by Rous sarcoma virus take up glucose and 2-deoxyglucose from their medium at a faster rate than untransformed cells although the rate of uptake of these sugars also depends on a cell's physiological state and in particular the rate at which it is dividing. This second observation raised doubts as to the relationship between enhanced uptake of sugars and transformation *per se*, but now Martin, Venuta, Weber and Rubin (*Proc. US Nat. Acad. Sci.*, **68**, 2739; 1971) have, by exploiting the temperature sensitive mutant T5 of Rous sarcoma virus isolated by Martin (*Nature*, **227**, 1021; 1970), shown that the increased rate of uptake of 2-deoxyglucose by transformed cells indeed depends on the expression of the transforming Rous sarcoma genome.

They report that when chick cells transformed by Rous virus and untransformed cells are growing at the same rate the transformed cells take up 2-deoxyglucose at a rate which is three times faster than the untransformed cells. Cells transformed by the mutant T5 and cultured at the permissive temperature of 36° C behave like cells transformed by wild type virus. But when mutant transformants are shifted to the nonpermissive temperature, 42° C, the rate at which they take up this sugar falls, without any detectable lag, such that by 12–24 hours after the shift the rate is that of untransformed cells. And when the transformants are returned to 36° C their rate of uptake once more increases. In short, transformed cells growing in the same conditions as untransformed cells exhibit a faster rate of uptake of 2-deoxyglucose and this difference depends, however indirectly, on the continued expression of the transforming Rous sarcoma genome. Furthermore, as experiments with cytosine arabinoside prove, the enhanced uptake of sugars by transformed cells is not dependent on DNA synthesis.

The mechanism which regulates the rate at which sugars are taken up by cells may well involve changes in the chemistry of the cell surface, a most fashionable subject for investigation among tumour virologists these days. Sachs and his colleagues, for example, report in the same issue of the *Proceedings* (*ibid.*, 2748) their latest experiments with concanavalin A and other lectins. They claim that SV40 transformed cells cultured at 24° C are much more readily agglutinated by concanavalin A than untransformed cells but at 4° C this difference between transformed and untransformed cells cannot be detected;

neither are agglutinated. At both 24° C and 4° C, however, both transformed and untransformed cells bind the same amounts of concanavalin A. Furthermore, after exposure to trypsin at 24° C untransformed cells are agglutinated by low concentrations of concanavalin A but after exposure to trypsin at 4° C neither transformed nor untransformed cells are agglutinated by low concentrations of this lectin.

From these data Inbar, Ben Bassat and Sachs argue that the sites which bind concanavalin A are not affected by temperature changes but the component of these sites which determines agglutina-

tion is temperature sensitive and transformation sensitive. The agglutination sites may well be associated therefore with some specific metabolic activity. Inbar *et al.* comment that this conclusion does not hold for two other lectin binding sites, those for wheat germ agglutinin and soybean agglutinin, which are not apparently temperature sensitive. And what is perhaps even more intriguing, Sachs and his colleagues remark that there is a correlation between the activity of the component of the concanavalin sites that is involved in agglutination and the malignancy of a cell; but that is to be another story.

T Cell Activation by Histocompatibility Antigens

THE general concept that lymphocytes of the mouse can profitably be classified as either T or B cells is now widely accepted. T cells are easily defined as those lymphocytes which have undergone differentiation in the thymus; their precursors moved to the thymus from either the bone marrow in an adult or an equivalent haematopoietic organ, probably the liver, in the foetus. The definition of B cells is less easy because it is by no means certain whether the mature B cell arises in the bone marrow or from a precursor cell which must leave the marrow to undergo proliferation and specific differentiation elsewhere. Functionally, however, the B cell seems, unlike the T cell, to have the capacity to differentiate into an antibody secreting cell and thus in spite of its slightly murky origins it can usefully be delineated as a cell species.

The functional characteristics of T cells are still a matter of some dispute and the arguments concerning them touch on the fundamental question of whether the immune process is instructive or selective. Most immunologists favour some form of selective mechanism, whereby an immune response proceeds because of selection from a heterogeneous cell population of those cells best equipped to deal with a particular antigen. The nature of the heterogeneity in this last instance is one of the central problems of immunology. Sprent and Miller, in an article in next Wednesday's *Nature New Biology*, study these problems and reveal how the careless adoption of a word can lead to unorthodoxy.

The Australian school of lymphocyte function has contributed much to the literature in recent years. Among their efforts has been the demonstration that when thymocytes along with an antigen, often heterologous erythrocytes, are injected into mice which have been lethally irradiated, the injected cells react to the antigen by blast cell transformation; when transferred, along

with more antigen, from the primary host spleen into a secondary irradiated animal the reacting cells display a specific capacity to cooperate in the ensuing immune response. The procedure at one time was referred to as "education". The full semantic horror of this nomenclature has now been realized, and Sprent and Miller offer "activation" as the preferred alternative.

Sprent and Miller describe the injection of parental strain thymocytes or thoracic duct lymphocytes into lethally irradiated F₁ hybrid mice. The injected cells proliferate in response to the antigens, foreign to them, of the other component of the hybrid and, after a period of intensive activity in the spleen and mesenteric lymph nodes, blast cells appear in the thoracic duct lymph.

These primed cells, when transferred to a second similar hybrid recipient, are capable of responding more quickly than a comparable unprimed thoracic duct lymphocyte population and, more interestingly, are much less capable of responding to a third party antigen—in an appropriate hybrid recipient—than are unprimed cells. The process of activation thus either involves selection of a specifically reactive cell population or it involves rapid restriction of an initially wider reaction potential.

It is interesting that activated parental cells collected from the thoracic duct of F₁ irradiated mice did not induce a splenomegaly reaction when injected into appropriate newborn F₁ recipients, and it was impossible to demonstrate the activated state beyond second transfer into irradiated F₁ recipients. This finding, which suggests a restriction on the proliferative capacity of T cells in response to continued antigenic stimulus; contrasts with the suggestion (Askonas *et al.*, *Proc. US Nat. Acad. Sci.*, **67**, 1398; 1970) that B cell populations have a capacity for repeated response to antigenic stimulus during a series of transfers in irradiated host mice.

Dental Plaque and Oral Health

D. F. G. POOLE & H. N. NEWMAN

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Oral diseases in man, such as periodontitis and dental caries, are not caused by single pathogenic organisms but appear to be the result of the complex biological interactions of the various organisms of which dental plaque is composed.

DISEASES of the teeth and their supporting structures are more widespread than any other disease. Chronic periodontitis, the principal cause of tooth loss, is a chronic inflammatory process involving gradual destruction of the supporting tissues of the teeth, and almost as prevalent is dental caries, the familiar tooth decay. In spite of continuing, intensive research, we are, in some respects, as far away as ever from a clear understanding of the aetiology, pathology and prevention of these two diseases. Perhaps the most intriguing aspect concerns a factor common to both diseases: the dental plaque.

It is now more than seventy years since the terms "gelatinous microbial plaques" and "feltlike mass" were introduced^{1,2} to describe the closely-packed mass of microorganisms present on the natural erupted tooth surface. Since that time, extensive effort has failed to implicate any single one of its constituent species as being the sole cause of either disease in man.

Host-Flora Relationships

It is possible that in our assessment of plaque we have failed to consider it as forming just one part of the body flora. This flora does not normally produce disease but, on the contrary, maintains a commensal or symbiotic relationship with the human host and is involved in several functions, including the digestive processes and the prevention of the establishment in the body of alien pathogens. If we extend this concept to other fields of microbiology, we soon discover that not only is plaque unexceptional, but that most surfaces have their own individual flora, a balanced microbiota living in dynamic equilibrium with its host. Many conclusions in bacteriological studies are based upon the activities of organisms grown in pure culture and it is worth emphasizing that organisms in their natural environment are often closely related to one another physically and tend to exhibit interdependence to a greater or lesser degree. Conclusions drawn from such measurements as the rate of reproduction of organisms in pure culture probably bear no relation to the state of affairs pertaining in a "natural" habitat. Recently it has become apparent³ that the rate of turnover of organisms in plaque may be less than that of organisms grown in pure culture under optimal metabolic conditions.

Microbial Communities

Plaque may represent a primitive example of community development, that is, of individual unrelated organisms living

together for their mutual benefit. Certainly the organisms in plaque are packed as closely together as those in a centrifuged colony of a pure culture^{4,5}. It would seem reasonable to suggest that the evolutionary process has led to a situation in which many different species of microorganisms have developed the capacity to live commensally or symbiotically with one another in communities such as the plaque, despite very close spatial relationships. Recent freeze-etch studies in our own laboratory would seem to indicate that this close packing is not artefactual, because the rapid freezing involved averts shrinkage due to dehydration.

Plaque Structure

Relatively little information about the structural organization of plaque is at present available. Its outstanding structural feature—that is, filaments orientated parallel to each other and at right angles to the tooth surface—was first noted by Williams⁶. Observations in our laboratory on paraffin sections, and using scanning, freeze-etch and transmission electron microscopy, indicate that smaller organisms are constrained to grow between filaments and may become attached to them, giving rise to the appearance sometimes described as *Leptothrix racemosa*. Ultrasonication for periods of up to 0.5 h has demonstrated the firmness of attachment of coccal and other forms to filaments⁶. This relationship is probably responsible for the appearance of "rosettes" on electron micrographs of the outer (salivary) surface of plaque, where a group of coccal forms is arranged around a central filamentous organism⁶⁻⁸.

Structure and Function

Provided that one accepts the initial random distribution of organisms in plaque, the close packing to which we have alluded would seem to imply the existence of one or both of two phenomena in the crucial stagnation sites implicated in caries and chronic periodontitis. Either the same organisms undergo a change in their metabolic pathways or different organisms become active because of a change in environment. Anaerobes, rather than aerobes, tend to be favoured by the increasing stagnation and decreasing oxygen tension and most plaque organisms are, in fact, facultative anaerobes^{9,10}, possessing both acidogenic and proteolytic potential. This consideration becomes of greater significance in the light of work in progress in Bristol and elsewhere, which would seem to suggest that the structure of plaque changes as it approaches the contact area or gingival margin but tends to show relatively constant structural features for a given thickness and for a given distance from the stagnation site. As the area in question becomes gradually less accessible to cleansing forces, it would appear that the undisturbed plaque increases in thickness and that, during this process, organisms at the enamel surface align themselves parallel to each other and at right angles to the tooth surface, and grow directly towards the plaque-saliva interface (presumably because this method of growth is suited to their nutrition^{6,7}). The fact that the site below the contact area between teeth is the most stagnant on enamel smooth surfaces must contribute to the known onset

of both caries and inflammatory periodontal disease in this region. With regard to stagnation sites, it is of interest that, in peoples living on crude diets, adjoining approximal surfaces frequently show marked wear facets indicative of heavy masticatory forces. This wear reduces the interstitial stagnation sites and also the areas of approximal tooth surface available to plaque. At the same time the heavy masticatory activity eliminates pits and fissures on occlusal surfaces, further reducing potential stagnation sites. Thus the low caries incidence in such peoples is related to both eating habits and low, refined carbohydrate intake. The significance of this would seem to be that the advent of a diet containing foods lacking in fibrous texture and overburdened with fermentable carbohydrate has been the principal factor contributing to the production of a focal point, interstitially, for the initiation of the two disease processes under discussion. Fissure plaque would seem to differ essentially from smooth surface plaque only in the limitations imposed on its size by its anatomical site^{11,12}.

Acid and Caries

The principal problem in plaque research has always been to explain its involvement in the production of caries and chronic inflammatory periodontal disease. Since the early work of Miller¹³ the concept of acid demineralization as the essential feature in the production of the carious lesion remains unchanged. It has been demonstrated¹⁴ that plaque lactobacilli and some streptococci form more acid in media containing enamel or dentine than in control cultures not containing tooth substance. More than one acid is, however, produced in plaque, and by many different organisms^{10,15-18}. Lactic acid has frequently been cited as the principal causative agent in caries, but it has been shown recently^{15,17,18} that other organic acids may also make important contributions.

Recent work¹⁹ on the destructive mechanism in dental caries has shown that the dividing line between acid demineralization and chelation may be much finer than was previously thought to be the case. In addition, attention has been drawn to oxidation-reduction potentials²⁰, electrolysis (P. Critchley, personal communication, 1970) and electrical potentials^{21,22}, as well as straightforward diffusion phenomena, as factors relevant to the pathogenesis of caries. It has been suggested²³ that, in a normal healthy mouth, slight mineral loss due to acids generated in the plaque is followed by mineral deposition. Under cariogenic conditions, dissolution is greater than deposition and one way of helping to boost the restorative role of the plaque might be the precipitation of insoluble calcium salts on the enamel surface, especially in stagnation areas. It has been suggested^{24,25} that the incidence of caries-like lesions in animals other than man points to an aetiological mechanism other than the production of acid from refined carbohydrate. The incidence of caries in animals is, however, extremely low and caries in other than "civilized" man has been shown to have a different pathogenetic basis²⁶, often being secondary to fracture of worn enamel and resultant food impaction.

The phenomenon of biogenic acid dissolution of mineral is not confined to the human oral cavity. Other workers^{27,28} have stressed the biologically fundamental nature of acid dissolution of minerals from an evolutionary standpoint. It has been noted²⁵ that certain marine organisms can bore into rock, shell and coral, and that living forms as different as algae, sponges, flatworms and snails are able to dissolve calcium-containing and other minerals chemically. The pre-eminence of phosphate as a limiting factor in cell metabolism has also been emphasized^{25,27}.

The use of elements such as phosphorus in the production of high energy bonds for metabolic requirements is well known. It has been suggested²⁹⁻³⁴ that the typical calcium

phosphate skeleton evolved originally as a simple means of localizing phosphate for energy purposes. An increasing body of evidence is becoming available which would seem to indicate that the production of acid within plaque is closely related to the requirements of plaque microorganisms for phosphate. Thus it has been found³⁵ that plaque inorganic phosphate levels are inversely proportional to caries incidence and that a high flow rate of parotid saliva appeared to be related to higher plaque phosphate levels and a lower incidence of caries. It has been shown³⁶ that acid production increases with thickness of plaque and³⁷ that plaque bacteria considerably modify the pattern of acid attack.

Our calculations show that only an infinitesimal amount of acid is required to produce the degree of demineralization that occurs in an average carious lesion—far less than is normally available in impacted food debris or as a result of microbial metabolism in the established plaque. A clearer explanation is hindered by the multiplicity of phenomena involved. At all events, the remineralization, which is a feature of arrested caries, would seem to indicate that demineralization and remineralization are usually in equilibrium. It is conceivable that calcium and phosphorus removed from the tooth by bacterial activity under non-pathological circumstances are replenished from the saliva, and that, although enamel as such possesses no physiological capacity for repair, salivary calcium and phosphorus probably constitute a very efficient repair mechanism³⁸.

Polysaccharides in Plaque

Considerable attention has recently been focused on yet another biochemical feature of plaque, its intra- and extracellular polysaccharide content, especially the highly branched dextrans. Plaque dextrans are now regarded as having two chief functions: the maintenance of the structural integrity of plaque by their inherent stickiness and high degree of branching, and their use as an energy storage product when the supply of simple sugars and laevans is exhausted. This view of the function of dextrans and associated polysaccharides in plaque metabolism may, however, have been oversimplified. In general, biochemical end-products may be regarded as the result of particular metabolic pathways aimed at the survival of the organisms involved. Thus it has been suggested^{3,38} that least dextran is formed under conditions most favourable for bacterial growth. It has also been proposed³⁸ that dextran might be used by bacteria as a means of concentrating ions or other essential nutrients. (Attempts are now being made to synthesize a particular polysaccharide in commercial quantities, for use in dealing with water pollution; this consists of glucose and some galactose, derived from the pseudomonad *Zooglea ramigera*, and is useful because of its ability to adsorb large amounts of metal ions and organic material³⁹.) Other workers have noted the relative inertness of plaque dextrans, and the extent to which they limit intercellular diffusion. The presence of polysaccharide matrices around individual organisms in pond slime has been described⁴⁰, and it has been suggested that, by means of this "shell", individual microorganisms are able to obtain physical and chemical protection from noxious agents in the environment. The last of these findings may be of considerable importance in plaque metabolism, because concentrations of sucrose—that highly cariogenic agent—inhibit most bacteria when present in excess.

Thus the information at present available suggests that plaque bacteria produce dextran and similar polysaccharides to deal with the problem of large quantities of fermentable carbohydrate and, possibly, also acid end-products, and to bind essential organic and inorganic nutrients which are only present in small quantities. In these circumstances, the viability of inner plaque may depend upon the diffusion of

nutrient material along filaments rather than through the interbacterial matrix⁶.

Chronic Periodontitis

Organisms which are farthest removed from the saliva-plaque interface are also at the greatest distance from a source of readily available nutrients²⁵. Attention has been drawn⁴¹ to the ability of plaque organisms to utilize whatever substrate is available, and it has been suggested⁴¹ that metabolism of a proteinaceous substrate would result in an alkaline environment favouring calcium formation, whereas the presence of fermentable carbohydrate would favour the production of an acid environment and caries. It has been pointed out previously that the two disease processes are initiated in close proximity to one another on the smooth surfaces of teeth. If the diet of the host contains little fermentable carbohydrate, mouth organisms must be dependent for their growth and reproduction on products of saliva, epithelium, gingival fluid and food debris. Thus the most gingivally situated plaque is in relation to an epithelium with a high rate of turnover and it might be expected to produce the agents which will also be most likely to initiate chronic periodontitis^{42,43} because of their digestion of epithelial protein.

In the light of recent findings^{3,38} it seems most likely that, in the deeper layers of plaque, there is frequently insufficient nitrogen available for cell growth and division, and that the consequence of this metabolic blockage is a build-up at each stage of the process; there is, therefore, an accumulation of acids and polysaccharide where fermentable carbohydrate is present. The only readily identifiable product is the polysaccharide and this may explain why attention has so far been directed at the polysaccharide rather than at an understanding of the underlying metabolic implications of its presence. When fermentable carbohydrate is not present, damage to the teeth as a result of caries becomes very unlikely. The ubiquitous nature of plaque compared with fermentable carbohydrate might possibly explain why chronic periodontitis is more widespread than caries.

Conclusions

It would seem to be a reasonable proposition that the natural tendency for organic material, both biotic and abiotic, to be adsorbed on inorganic surfaces has favoured cell growth. This appears to be reflected in the situation existing in the mouth, where bacteria and salivary pellicle are being deposited continuously on available erupted enamel surfaces. In this way organic nutrients may be localized to the advantage of the organisms concerned.

Similarly, bacterial phosphate requirements seem to be favoured by their adsorption on tooth surfaces. There may be a link with a possible mechanism of enamel "protection", whereby mineral lost as a result of microbial activity is replaced by salivary calcium and phosphate. In the evolutionary scale, the tendency has been for higher organisms to acquire salivary glands and to lose numbers of dentitions; this may be significant, not only as far as mastication, which is a function of mammals, is concerned, but also in relation to maintenance of the integrity of the tooth surface.

The caries process may be regarded as due to the effects of organic acids normally used as energy sources in the production of proteins and other components essential to microbial cell growth and division. But carbohydrates as such represent potential energy, whereas the various acids represent kinetic energy and are involved in several stages of different biochemical cycles.

The onset of chronic inflammatory periodontal disease, on the other hand, may be attributed to the activities of bacteria which will utilize gingival epithelium as a substrate and will therefore damage the periodontium, unless the

nature of the diet and the oral hygiene of the patient are such that a build-up of plaque at the gingival margin is prevented.

Controversial though some of these concepts of plaque may seem, it is essential, in our opinion, to realize that we are dealing, not with a straightforward pathological entity, but with a complex ecological phenomenon, many of whose features are common to other microbial communities. This should, in turn, influence our approach to the treatment of caries and chronic periodontitis because it becomes a question, not of haphazardly and maybe dangerously interfering with the balance of the oral microbiota (a factor of considerable importance in the maintenance of health) but of modifying the diet or the plaque without the use of antiseptics, antibiotics or other agents which are likely to produce cures worse than the diseases.

Comprehensive reviews of the subject have recently been published^{44,45}.

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Chemical Constituents of Interstellar Clouds

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The application of organic chemistry to the interstellar medium has considerably heightened the appreciation of the complexity and variety of interstellar clouds. Results obtained during the past three years suggest that only a start has been made in the identification of the molecular constituents of these clouds.

RECENT attempts to interpret the intensity and distribution of interstellar molecules and their isotopic counterparts have led to some preliminary conclusions about the environment in which these molecules exist. And the predominance of organic species and their similarity to the products obtained in the synthesis of amino-acids in the study of the origin of life suggests a very close parallel between interstellar clouds and prebiotic chemistry. These are the directions in which the study of interstellar molecules is proceeding. The research is an interesting overlap of astronomy, physics, chemistry and biology and there are clearly exciting contributions to be made to all these fields. In this article I shall review present knowledge about interstellar clouds and indicate where the most promising future developments are likely to occur.

Early Discoveries

The chief breakthrough occurred in late 1968 and early 1969 with the discovery of NH_3 , H_2O and H_2CO which occurred in rapid succession¹⁻³. Until that time only simple diatomics were known to exist in the interstellar medium (Table 1) and it was thought that the environment was characterized by very low densities and large fluxes of ultraviolet radiation and cosmic rays—very difficult conditions for the formation and preservation of complex molecular species. The presence of dust grains, however, apparently plays a very important role in the molecular evolution of these clouds. The dust grains may provide the catalytic surfaces on which the molecules can form as well as the shielding necessary to protect the molecules from photo-dissociation. The extinction and reddening of starlight have been known for some time and the dust, which is presumed to be responsible for this, is thought to be in the form of carbon or silicates with a size of about 0.1 μm . Very little else is known about the composition of these particles; their temperatures are about 10 K and the ratio of the density of dust to that of hydrogen is about 10^{-12} . The dust seems to be located along the inner edges of the galactic spiral arms in regions of high density consisting chiefly of molecular hydrogen. The dust, hydrogen and molecular clouds usually appear in relatively dense condensations which are apparently in the process of collapsing into stars and planetary systems. Hence the evolution of the molecular clouds is intimately related to the evolution of the relatively thin interstellar hydrogen gas into dense hydrogen burning stars.

Detection of Formaldehyde

The most important molecule to have been found in interstellar clouds is probably formaldehyde. Eight microwave lines of this molecule have been found and the 6 cm absorption line, in particular, appears in a large number of galactic sources⁴. The formaldehyde seems to permeate the galaxy, showing a preference for dusty regions. The behaviour of this molecule in some of the nearby dust clouds is particularly interesting. The molecule was detected in absorption in these clouds against the faint 3 K microwave background radiation, a very peculiar state of affairs in which the molecule is being



Fig. 1 Orion nebula. (Photograph from the Mount Wilson and Palomar Observatories.)

cooled or refrigerated below 3 K (ref. 5). The cooling occurs throughout these clouds and indicates a very general mechanism for pumping the formaldehyde. It was concluded that collisions with hydrogen molecules at a density of 10^3 cm^{-3} were responsible for the refrigeration⁶. In most of the other galactic sources the molecule seems to be in equilibrium with the 3 K microwave radiation. Presumably this is the result of the lower densities of 1 to 10 hydrogen atoms cm^{-3} in the interstellar medium.

One problem, as far as formaldehyde is concerned, is posed by the Orion nebula, a cloud about 10 light years across and 1,500 light years away (Fig. 1). It is usually the brightest object in the sky for molecular emission lines but the 6 cm absorption is quite weak⁷. The dark molecular cloud probably lies behind the bright emission nebula where the radio continuum originates. But why, then, does the formaldehyde not show up strongly in absorption against the 3 K background radiation? The formaldehyde is detected strongly in emission

at 2 mm in the centre of the nebulae⁸ and this emission requires a molecular hydrogen density of 10^5 molecules cm^{-3} in a region of size about 1 light year. The formaldehyde absorption indicates that the size of the molecular cloud is at least 10 light year extending chiefly to the south of the intense emission region. It would seem that somewhere in the cloud a strong absorption line could be produced at the density of 10^3 molecules cm^{-3} necessary for refrigerating the formaldehyde.

Hydroxyl Radicals

Studies of the distribution and excitation of the OH molecule have been carried on extensively since its discovery in 1963 (ref. 9). The molecule appears in absorption against a considerable number of galactic radio sources. Velocities of the clouds as measured in OH and H_2CO lines are similar and an

are about 10^8 cm^{-3} and indicate an object in the process of gravitational collapse. An interesting possibility is that the energy generated by the collapse is being radiated away by the maser emission process of the molecular cloud. In this case, through collisions with hydrogen molecules, the H_2O and OH are performing the important function of cooling the hydrogen cloud as it collapses into a protostar. The coincidence of the OH and H_2O maser in Orion with an infrared star in the densest part of the nebula strengthens this conclusion.

Carbon Monoxide

The CO molecule has a very stable triple bond which is difficult to dissociate and thus has a lifetime in an unprotected region of at least 1,000 yr compared with 30 yr for most other molecules¹¹. The CO molecule is present in very large regions

Table 1 Molecules Found in the Interstellar Medium

Year	Molecule	Symbol	Wavelength	Telescope	Initial discovery
1937		CH	4300 Å	Mt Wilson 100 inch	Dunham
1940	Cyanogen	CN	3875 Å	Mt Wilson 100 inch	Adams } Mt Wilson
1941		CH^+	3745–4233 Å	Mt Wilson 100 inch	Adams }
1963	Hydroxyl	OH	18, 6.3, 5.0 and 2.2 cm	Lincoln Lab 84 foot	MIT/Lincoln Lab
1968	Ammonia	NH_3	1.3 cm	Hat Creek 20 foot	Berkeley
1968	Water	H_2O	1.4 cm	Hat Creek 20 foot	Berkeley
1969	Formaldehyde	H_2CO	6.2, 2.1 and 1 cm; 2.1 and 2.0 mm	NRAO 140 foot NRAO 36 foot	University of Virginia, NRAO, University of Maryland and University of Chicago
1970	Carbon monoxide	CO	2.6 mm	NRAO 36 foot	Bell Labs
1970	Cyanogen	CN	2.6 mm	NRAO 36 foot	Bell Labs
1970	Hydrogen	H_2	1100 Å	UV rocket camera	NRL
1970	Hydrogen cyanide	HCN	3.4 mm	NRAO 36 foot	University of Virginia and NRAO
1970	X-ogen	?	3.4 mm	NRAO 36 foot	NRAO and University of Virginia
1970	Cyano-acetylene	HC_3N	3.3 cm	NRAO 140 foot	NRAO
1970	Methyl alcohol	CH_3OH	36 and 1 cm; 3 mm	NRAO 140 foot	Harvard
1970	Formic acid	CHOOH	18 cm	NRAO 140 foot	University of Maryland and Harvard University
1971	Carbon mono-sulphide	CS	2.0 mm	NRAO 36 foot	Bell Labs and Columbia University
1971	Formamide	NH_2CHO	6.5 cm	NRAO 140 foot	University of Illinois
1971	Silicon oxide	SiO	2.3 mm	NRAO 36 foot	Bell Labs and Columbia University
1971	Carbonyl sulphide	OCS	2.7 mm	NRAO 36 foot	Bell Labs and Columbia University
1971	Acetonitrile	CH_3CN	2.7 mm	NRAO 36 foot	Bell Labs and Columbia University
1971	Isocyanic acid	HNCO	3.4 mm; 1.4 cm	NRAO 36 foot	University of Virginia and NRAO
1971	Hydrogen isocyanide	HNC	3.3 mm	NRAO 36 foot	University of Virginia and NRAO
1971	Methyl-acetylene	$\text{CH}_3\text{C}_2\text{H}$	3.5 mm	NRAO 36 foot	University of Virginia and NRAO
1971	Acetaldehyde	CH_3CHO	28 cm	NRAO 140 foot	Harvard University
1971	Thioformaldehyde	H_2CS	9.5 cm	Parkes 210 foot	CSIRO, Australia

approximate abundance ratio $\text{OH}/\text{H}_2\text{CO} \sim 30$ is obtained⁴. The abundance of hydrogen relative to formaldehyde is $\text{H}/\text{H}_2\text{CO} \sim 10^8$. These ratios vary considerably in different parts of the galaxy and almost all that can be said is that OH may be somewhat underabundant whereas the abundance of H_2CO is close to what would be expected from the atomic abundances of the constituent atoms.

In the nearby dust clouds the OH shows up in emission, thus indicating temperatures of about 10 K (ref. 10)—rather low by comparison with the typical hydrogen cloud temperature of 100 K; at the same time the formaldehyde is being cooled below 3 K. Presumably the same process heats the OH and cools the formaldehyde. In regions much higher in density than the 10^3 molecules cm^{-3} of the dust clouds, the OH is pumped into very intense maser emission. A similar situation occurs for the H_2O molecule. The sizes of these regions are quite small (~ 1 AU) and the amount of energy involved is quite large ($> 10^{30} \text{ erg s}^{-1}$). The densities required

of most sources and apparently does not require the protection of dust grains¹². This makes it an ideal molecule with which to map the structure of the Galaxy. It is also apparently very dense and generally opaque in the microwave line; this fact and the low dipole moment lead to the conclusion that it is a good indicator of the kinetic temperature in a cloud. By contrast the HCN molecule has a rather large dipole moment and will therefore have a stronger coupling to the radiation field¹³. The densities required to excite the CO molecule by collision are 2×10^3 hydrogen molecules cm^{-3} compared with 10^6 molecules cm^{-3} for HCN (ref. 14).

Isotopic Counterparts

The ^{13}C and ^{18}O isotopes of OH, H_2CO , CO and HCN are important for studying the extent to which nuclear burning processes have changed the isotopic abundances in various parts of the Galaxy. They also provide data about the extent

of line saturation in lines which have a high opacity. The terrestrial abundance of $^{12}\text{C}/^{13}\text{C}$ is 89 but the formaldehyde is found to have an anomalous abundance ratio for the galactic centre absorption line of $^{12}\text{C}/^{13}\text{C} = 11$ (ref. 15). Recently the ^{18}O line of formaldehyde was detected in Sgr B2 and yielded an overabundance of ^{13}C relative to ^{18}O by a factor of two (ref. 16). This can be interpreted in terms of an abundance ratio $^{12}\text{C}/^{13}\text{C}$ of 45 and an opacity τ of 4.5. Interferometer observations of the source Sgr A give $^{12}\text{C}/^{13}\text{C} = 25$ and $\tau = 2$ (E. B. Fomalont and L. N. Weliachew, to be published).

There are at least two unidentified lines in the millimetre range around 90 GHz. The first is called X-ogen (ref. 17) and is possibly a line of HCO^+ (ref. 18). The second is tentatively identified as HNC based on a calculated frequency which falls close to the observed line (L. E. Snyder and D. Buhl, to be published). Neither of these molecules is stable in the terrestrial environment, but the interstellar medium may be a perfect place to manufacture and store such unusual species of radicals and ions. Undoubtedly there will be many more unidentified lines as receiver sensitivity increases, particularly in the millimetre range. The matching of a single line with a molecule is about 99 per cent reliable at the present density of microwave lines. Increased sensitivity will crowd the spectrum with lines and make it necessary to find several lines of a molecule before being certain of its identification. This can be done by searching for a second transition with different quantum numbers, detecting the ^{13}C isotope of the molecule or trying to resolve hyperfine splitting in the line in a source with a small Doppler width. Only two molecules, OH and H_2CO , have been identified by all these methods.

Larger Molecules

The larger organic molecules have generally only been found in the galactic centre source Sgr B2. This is probably due to the greater size of the region and possibly to the more efficient production of molecules in the galactic centre. The energy levels of these molecules are compressed because of the larger mass and a significant number of levels are thus populated, with the line frequency generally increasing at higher levels. The lines will usually be stronger at these higher levels and hence easier to detect. Several molecules (HNCO , OCS and CH_3CCH) have shown this tendency¹⁹ and it therefore seems that the future detection of heavy molecules will come from higher level transitions with frequencies in the millimetre range. This is particularly true because the principal improvements in receiver sensitivity can be expected at these wavelengths²⁰. The far infrared may be important for detecting molecular vibrational transitions as well as additional rotational transitions of light molecules such as H_2O .

The optical observations of the 1930s revealed several lines which were subsequently identified as the radicals CH, CH^+ and CN. Several interstellar diffuse bands have been observed, however, and particularly prominent is a line at 4430 Å (ref. 21). All attempts to identify these bands have failed. The porphyrin molecule has been suggested as a possible source of sixteen of the twenty-five bands²² but the identification is quite controversial and needs further confirmation. It seems that the radio spectrum will also soon contain a considerable number of unidentified lines. The interstellar medium may very well contain molecules, radicals and ions with unusual structures not commonly encountered on Earth.

Origin of Life

Is there a connexion between the interstellar molecular clouds and the origin of life? It is difficult to establish a direct connexion, but the similarity of the organic molecules produced in laboratory experiments²³ to the molecular composition of interstellar clouds suggests a dominant direction

in the chemical synthesis which proceeds despite the very different environment of the cool, low density interstellar clouds. These molecular clouds are believed to be located in regions where an important stage of evolution is taking place. The collapse and formation of a star from the gas in a diffuse nebula take place in a relatively short time scale and it is precisely at this time that the molecules appear in these condensing clouds. They probably provide the early atmospheres of planets which presumably form at the same time. Once the star evolves, the remainder of the condensing cloud is blown away and any molecules left will probably be dissociated. The Earth is assumed to have lost its early hydrogen rich atmosphere so most of the primordial gas will also be lost.

Some extra-terrestrial organic material does, however, fall on the Earth. The discovery of abiological amino-acids in the Murchison meteorite²⁴ indicates that complex organic material from other parts of the solar system often adds very small amounts of unusual amino-acids to the Earth's biosphere. On a larger scale the collision of a comet with the Earth may add considerable amounts of primordial organic molecules. Such collisions were probably relatively frequent during the first 10^9 years of the Earth's history and comets are thought to be large frozen samples of the original solar nebulae which orbited the Sun at considerable distances. Several develop highly elliptical orbits which bring a few large comets each year into the vicinity of the Sun and the Earth. One can only conclude that, although the collision of a comet with the Earth may have been a relatively frequent event, it is uncertain whether sufficient amounts of organic material would have been added to influence the origin of life or affect its subsequent evolution.

The important parallels appear to be between the formation of interstellar molecules and the synthesis of amino-acids in prebiological chemistry experiments. It is here that the key to the evolution of interstellar molecular clouds lies.

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South Polar and Equatorial Differences in Central Peaked Martian Craters

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Central peaks in Martian craters in the south polar region occur more frequently than their equatorial counterparts and the peak frequency statistics and crater morphologies imply that preferential peak production has taken place.

We report the results of a preliminary study of the distribution of central peaked Martian craters based on photographs taken by Mariner 6 and Mariner 7; this study provides information about the origin of these craters and about the geological processes occurring on the surface of Mars. By comparing our results with statistics of central peaks in lunar craters¹, we can deduce whether or not similar crater forming and eroding processes have taken place on Mars and on the Moon.

Theories of the origin of central peaks in craters include formation by impact, volcanic activity, permafrost (pingos) and uplift following isostatic compensation. Mechanisms for the erosion of such peaks include meteoritic bombardment, a gradual relaxation of the structure through creep and—in the case of Mars—the action of wind and water (ice) especially through freeze-thaw cycles.

Identification and Measurement

Regions of low solar illumination were studied so that the maximum number of central peaks could be detected. For Mariner 6 and 7 the Martian equatorial region from about latitudes 10° to 20° S (frames 6N19, 21, 23 of Deucalionis Regio) and the south polar region at $\geq 70^\circ$ S (frames 7N11, 13, 15, 17, 19) were suitably illuminated. These were divided into regions of comparable solar illumination along lines 10°, 20° and 30° from the terminator and separate crater peak investigations were carried out within each of these regions. In this way comparable lower limits in elevations (or slopes) could be expected in features seen in corresponding equatorial and polar areas.

Although equatorial crater identification was hindered by resolution limits and lack of contrast, observations in the south polar areas were more difficult because of partial rim destruction, surface obscurations and apparently rough terrain.

Crater peak recognition was more difficult than crater identification because peaks are smaller than craters, peak forms are more diverse than crater forms, and peaks are more adversely affected by surface contrast deficiencies. Peaks were required to exhibit a bright region in the direction of the Sun and a dark region in the opposite direction, to give the impression of positive topographic relief. This requirement minimizes the chance of mistaking possible frost accumu-

lations² on crater floors for central peaks. In all but a very few instances unambiguous albedo variations suggesting peaks were discernible. The few questionable cases do not substantially affect the data or the conclusions drawn from them.

Many examples of Martian central peaks can be seen in the orthographic projection of Mariner frame 7N19 (Fig. 1). In the upper left part of Fig. 1 a massive dome formation of diameter ~ 150 km with a central peaked crater can be seen.

The crater diameter is ~ 50 km and the central peak is ~ 20 km wide. Such a broad central peak is atypical of those seen on the Moon. The apparent partial remains of a large ring structure (~ 800 km in diameter) can also be seen in the central

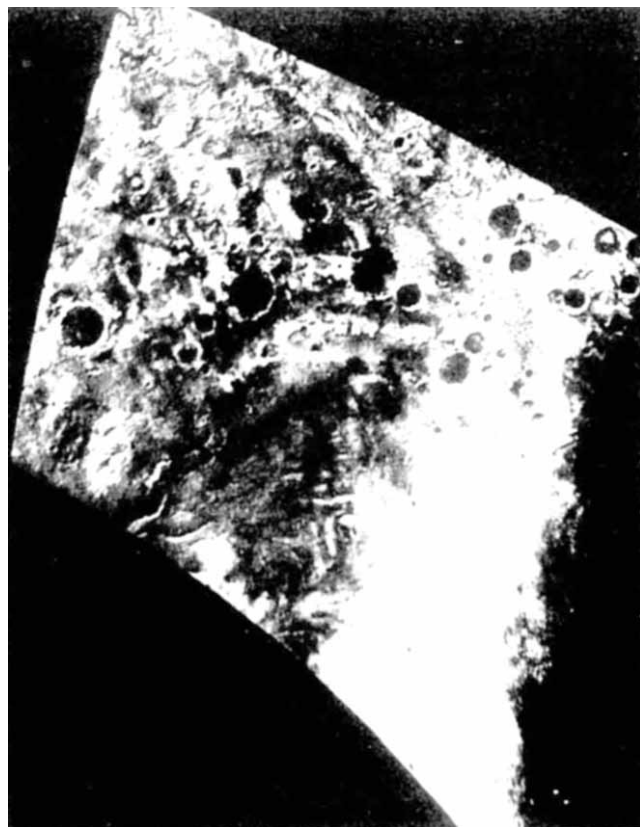


Fig. 1 Orthographic projection of Mariner frame 7N19 showing numerous craters with central peaks. In the upper left, a massive dome formation with a broad central peaked crater can be seen. In the centre, the partial remains of a large apparent ring structure can be identified.

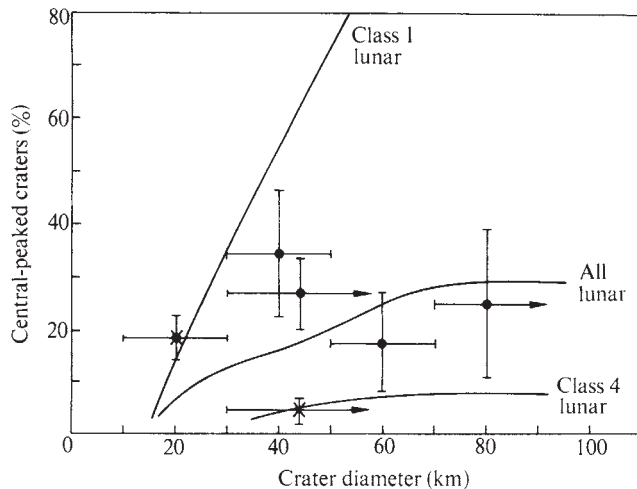


Fig. 2 Percentage of craters with central peaks as a function of crater diameter for Martian south polar and equatorial craters and lunar craters¹ in various stages of preservation. ×, Equatorial craters; ●, polar craters.

portion of Fig. 1. If this arc does indeed represent what was once a ring structure it would suggest that Mars, like the Moon, experienced catastrophic imbrium-like impact events early in its history.

Crater diameters were measured between rim summits along the direction of least foreshortening and account was taken of the variation of scale within the frames. Cumulative crater size-frequency distributions were compiled from the crater counts and diameter measurements; these distributions are in agreement with those previously observed³ and show no significant variation with solar illumination angle within the range 0° to 30°.

Central Peak Statistics

The smallest crater in which a peak was clearly resolvable had a diameter of ~10 km. This was also the lower limit of crater diameters included in the statistical study of lunar peaked craters¹. In the south polar region, thirty-nine craters with central peaks were observed out of a total of 179 craters with diameter >10 km, and in the equatorial region 28 craters with central peaks were found out of a total of 203. The crater counts are listed in Table 1 as a function of crater diameter.

Table 1 South Polar and Equatorial Statistics of Central Peaked Martian Craters

	Crater diameter (km)	No. of peaks	No. of craters	% of peaks
South polar	11-30	20	108	18.5
	31-50	11	32	34.4
	51-70	4	23	17.4
	> 71	4	16	25.0
Equatorial	11-30	25	134	18.6
	> 31	3	69	4.3

The proportions of all craters with central peaks in the south polar and equatorial regions of Mars are $22 \pm 4\%$ and $14 \pm 3\%$, respectively. The percentage in the equatorial region is consistent with interpretations⁴ of the Mariner 4 photographs at comparable latitudes—central peaks were reported in ~11% of the craters of diameter >10 km. But the low resolution of the Mariner 4 rendered both peak and crater identification much less reliable.

The Martian peak frequency is substantially greater than the 7% reported¹ for all lunar craters in the same size range.

These percentages for the Mariner 6 and 7 data are shown in Fig. 2, as a function of crater diameter, together with the percentages determined for lunar craters¹. There is a significant difference between relative frequency of south polar and equatorial peaked craters. For craters with diameter $D > 30$ km the frequency of central peaks in the polar region is six times that in the equatorial region and no central peaks were identified in the equatorial region in craters larger than 40 km in diameter. The fact that these frequencies each differ from a common mean by more than two standard deviations implies an important difference in either the origin or evolution of peaked craters in the south polar and equatorial regions. In this same diameter range the south polar frequency is in qualitative agreement with the frequency for all lunar craters. The equatorial frequency is four standard deviations lower than that of the combined lunar group but approximates that of class 4 lunar craters which are severely degraded and presumably among the oldest. There is a suggestion that the proportion of polar central peaks in the interval $30 < D < 50$ km exceeds that of the combined lunar craters. For craters with $D < 30$ km the frequencies of central peaks in the Martian polar and equatorial regions are nearly identical. Also, the frequencies in this diameter range are comparable with central peak frequencies in class 1 lunar craters but exceed by almost three standard deviations the frequencies in all lunar craters. Class 1 lunar craters have very sharp and complete rims and are presumably the youngest¹.

Excess and Agreement

To understand the south polar excess in the frequency of central peaked craters for $D > 30$ km and the agreement in the frequency statistics for $D < 30$ km we must consider the overall morphology of Martian craters. Two extreme types of Martian craters have been recognized³, small bowl-shaped ones and large flat-bottomed ones. The bowl-shaped craters predominate at diameters <15 km and show little evidence of modification, whereas flat-bottomed craters predominate at greater diameters and are significantly modified, with greatly subdued rims and generally unrecognizable secondary craters and ejecta blankets. The small bowl-shaped craters are clearly younger because they would have been degraded along with the ejecta blankets and ray systems of the larger craters if they had been created at the same time. And the absence of large fresh craters suggests either that the distribution of objects incident on Mars was deficient in large bodies compared with that of objects incident on the Moon, or that erosion is more efficient on Mars.

These descriptions of Martian crater morphology and the assumption that the origin of Martian central peaks is similar to that of lunar rebound peaks⁵ imply that the central peak frequency in craters of diameter >30 km should be small and in rough agreement with that of the degraded (class 4) lunar craters. Furthermore, the central peak frequency in the smaller craters ($D < 30$ km) should be comparable with that of the fresh (class 1) lunar craters. It can be seen from Fig. 2 that these conclusions are in agreement with the equatorial statistics and the south polar statistics for $D < 30$ km. For $D > 30$ km, however, the central peak frequency in the south polar region is significantly greater than that in the equatorial region and in class 4 lunar craters. This could suggest preferential peak formation in the south polar region.

A possible alternative explanation of the polar-equatorial differences in central peak crater statistics is preferential peak erosion in the equatorial region. This is consistent with the rough agreement between central peak frequency in south polar craters and all lunar craters but it is inconsistent with the qualitative observation that the Martian craters generally appear more degraded than lunar craters³. There is no evidence, however, that erosion has taken place preferentially in the equatorial region because the overall crater morphology is similar in these regions (in particular, the rims of the large craters appear to be equally subdued) and the population

indices of the cumulative crater size frequency distributions are nearly the same in this size range ($D > 30$ km) for both regions. We therefore conclude that preferential central peak formation has occurred in the south polar region.

From the limited coverage by Mariner 6 and 7 we cannot determine whether this preferential central peak production is a latitude effect or simply a regional variation. The similarity of the peak frequencies observed in Mariners 4 and 6 at widely separated equatorial regions would, however, suggest a latitude variation. If the phenomenon is latitude-dependent pingo formation might be the source of the peaks because Martian permafrost may be confined to polar latitudes⁶. But if the phenomenon is simply a regional variation, it may

be explicable in terms of volcanism or other mechanisms.

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Haemoglobin Constant Spring—A Chain Termination Mutant ?

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Haemoglobin Constant Spring is an unusual variant which comprises only 1–2% of the total haemoglobin in heterozygotes. It has α -chains which are 172 residues long instead of the normal 141, and when it is inherited together with an α -thalassaemia gene it gives rise to haemoglobin H disease.

Most human haemoglobin variants result from single amino-acid substitutions in one of the globin chains. Normal adult haemoglobin is made up of haemoglobin A (Hb A) which consists of 2α and 2β -chains ($\alpha_2\beta_2$) and haemoglobin A₂, the normal minor component, which has the formula $\alpha_2\delta_2$. The α -chains contain 141 amino-acids while the non- α -chains are 146 residues long. Each of the reported substitutions has been consistent with a single base change in the DNA which codes for the affected chain¹. In a few other variants (such as Hbs Freiburg and Gun Hill) one or more amino-acids have been deleted, probably during intragenic crossing over^{2,3}. Finally, in several abnormal haemoglobins (the haemoglobin Lepores and anti-Lepores) normal α -chains are combined with chains made up of the N-terminal residues of the δ -chain combined with the C-terminal residues of the β -chain or vice versa. These composite $\delta\beta$ or $\beta\delta$ -chains are also 146 residues long and have probably arisen by unequal crossing over between the closely linked δ and β -loci⁴.

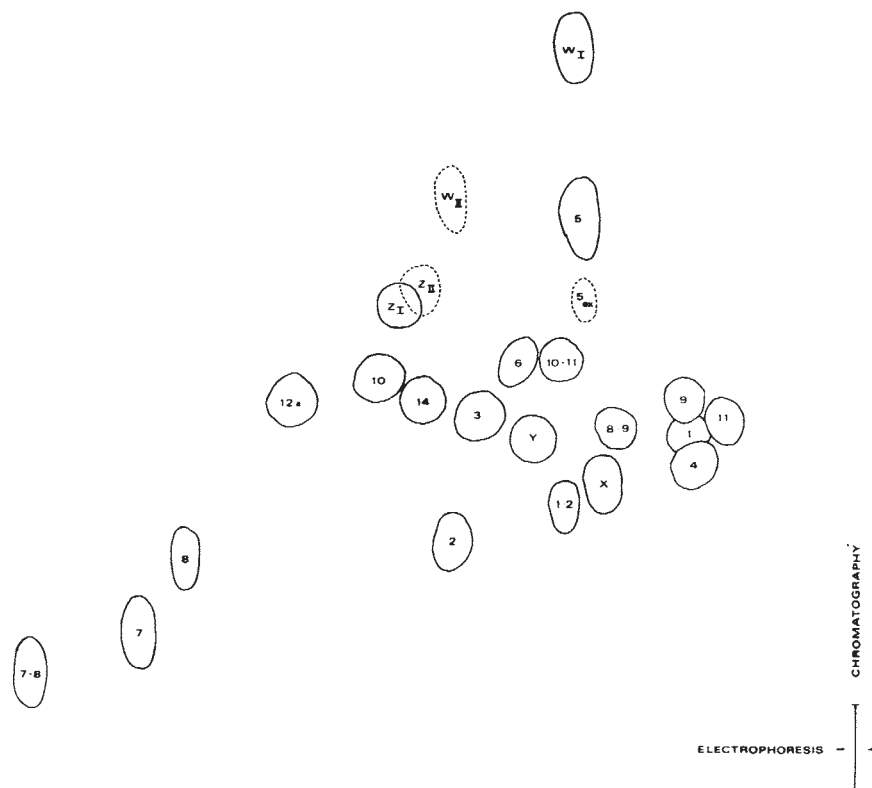
We report here a different type of human haemoglobin variant which has an additional thirty-one residues at the C-terminal end of the α -chain, apparently due to a type of mutation which differs from those previously responsible for the production of haemoglobin variants.

The new variant (Hb CS) was discovered in Constant Spring, Jamaica, in a large Chinese family in which three children have haemoglobin H disease, a disorder which is characterized by a moderately severe haemolytic anaemia associated with the presence of 5–20% Hb H (ref. 5) and variable amounts of haemoglobin Bart's. Hb H consists of 4 β -chains (β_4) while Hb Bart's is γ_4 ; both result from a reduced rate of α -chain production (α -thalassaemia) leading to the accumulation of excess β and γ -chains in the cell⁶. Haemoglobin H disease usually follows the inheritance of two α -thalassaemia genes, severe and mild, designated α -thalassaemia 1 and 2 (ref. 7). The α -thalassaemia 1 gene results in a complete suppression of α -chain synthesis⁸, whereas the α -thalassaemia 2 gene leads to a reduced production of α -chains. Usually in haemoglobin H disease the haemoglobin consists of A and H only, but in this family the affected children carried about 2% of slowly migrating haemoglobin (Hb CS) which resolved into two bands on starch gel electrophoresis⁹. About 1% of Hb CS was found in the children's father and several siblings, while the mother carried the α -thalassaemia 1 gene. The relative proportions of the two Hb CS components (Hb CS1 and Hb CS2) varied between samples but in fresh red cell lysates the more anodal fraction at pH 8.5 (Hb CS1) always exceeded that of Hb CS2; occasionally Hb CS1 was the only fraction observed. Full genetic and clinical details of this family⁹ indicate that the Hb CS gene can interact with the α -thalassaemia 1 gene to produce haemoglobin H disease. For this reason we have examined both the structure and rate of synthesis of Hb CS.

Structure

Pure Hb CS was prepared from the blood of a child with haemoglobin H disease and Hb CS. Haemolysates were made in a standard way¹⁰ and cleared by centrifugation at 20,000g for 30 min. A sample containing about 2 g of haemoglobin was dialysed against phosphate buffer¹¹, pH 7.12, and applied to a 2×30 cm 'Amberlite IRC 50' column at 4°C. After elution

Fig. 1 Superimposed tracings of fingerprints of tryptic digests of the α^{CS1} and α^{CS2} -chains. The two peptides derived from the C-terminal end of the α^{CS2} -chain are shown as broken circles.



of haemoglobins H and Bart's at 4° C, the column was allowed to equilibrate at 25° C and haemoglobins A and A₂ were then eluted. Hb CS remained as a tight band at the top of the column and was eluted with the same phosphate buffer made 0.3 M in NaCl. Hb CS prepared in this way was contaminated with less than 10% Hb A on starch gel electrophoresis. The yield of Hb CS1 was always greater than Hb CS2 when prepared in these conditions.

Globin prepared from the purified Hb CS fraction by acid-acetone precipitation was separated into its constituent chains by chromatography on CM-cellulose in 8 M urea/2-mercaptoethanol buffers as described previously¹². Two abnormal α -chain components (α^{CS1} and α^{CS2}) were observed in proportions corresponding to the two Hb CS fractions seen on starch gel electrophoresis, while the β -chains were identical to those of haemoglobin A. Fingerprints¹² prepared from trypsin digests of the aminoethylated derivatives of the two abnormal α -chain components (Fig. 1) showed that all the peptides normally found in α^A -chain digests were present and had the expected amino-acid compositions. In addition there were four extra peptides (W, X, Y and Z) present in both the α^{CS1} and α^{CS2} fractions, the compositions of which (Fig. 2) did not correspond with any tryptic peptides from human α , β , γ or δ -chains.

Studies on the fragments obtained from the α^{CS1} -chain by cyanogen bromide cleavage indicated that the additional peptide material extended beyond the normal C-terminal residue of the α^A -chain (141 Arg), and this was confirmed by the finding that the free arginine derived from Arg 141, and normally present on fingerprints of chymotrypsin digests of the α^A -chain, was missing in digests of α^{CS1} -chain, and had been replaced by three new arginine-positive peptides with compositions corresponding to residues 141–154, 155–160 and 166–168 of the α^{CS1} -chain (Fig. 2).

The additional trypsin peptides account for an extra thirty-one residues so that in Hb CS the α^{CS1} -chain is 172 residues long and has a molecular weight of 18,500. This agrees approximately with the value of about 20,000 found for the slower of the two bands observed on SDS-gel electrophoresis¹³ of Hb CS globin. Normal Hb A globin gave only one band with a mobility identical to that of the faster (that is, the β -chain) of

the two bands from Hb CS globin. The amino-acid sequence of the extra residues of the two α^{CS} -chains has been determined and is shown in Fig. 2. The difference between the two α -components lies in the absence of the C-terminal tripeptide Val. Phe.Glu in the α^{CS2} -chain, accounting for the two related peptides W_I and W_{II} found in the trypsin digests of the α^{CS1} and α^{CS2} -chains respectively. Peptides Z_I and Z_{II} presumably resulted from a weak trypsin split at the Arg-Pro bond at position 166–167. Since some conversion of α^{CS1} to α^{CS2} can take place in haemolysates in certain conditions (for example, on storage) it seems likely that the α^{CS2} -chain is normally derived from the α^{CS1} -chain, probably by the action of intracellular proteolytic enzymes.

Biosynthesis

The fact that α^{CS1} can be converted to α^{CS2} suggested that the low amounts (1–2%) of the Hb CS in the peripheral blood of our subjects might not be representative of the true rate of synthesis of the α^{CS} -chain. The relative rates of synthesis of haemoglobins A and CS were therefore examined in labelling experiments. Washed peripheral blood cells, containing from 5–10% reticulocytes, from the individuals heterozygous for Hb CS alone or for Hb CS and α -thalassaemia 1 were incubated with ³H-leucine or ³H-arginine for 5 min to 2 h (ref. 10). Cells were washed, lysed and the total "globin" precipitated by the acid-acetone method. The distribution of radioactivity in the globin chains after separation by CM-cellulose chromatography in 8 M urea was then determined (Table 1). In the samples from individuals doubly heterozygous for Hb CS and α -thalassaemia 1 the total radioactivity incorporated into the β and γ -chains exceeded that incorporated into the combined α^A and α^{CS} -chains by a factor of approximately 2 to 1, a ratio similar to that found in haemoglobin H disease⁶. Furthermore, the specific activity of the β -chain exceeded that of the α -chains, indicating that there is less unlabelled β -chain present than would be expected from its rate of synthesis. These findings, caused because excess β -chains precipitate in the red cell and are removed in the circulation, are also typical of haemoglobin H disease⁶. In a further experiment reticulocytes from one of the individuals heterozygous for α -thalassaemia 1 and Hb CS

Table 1 Radioactivity Incorporated into Globin Chains after Incubation of Reticulocytes of an Individual heterozygous for α -Thalassaemia 1 and Hb CS

Experiment	Isotope	Incubation time (min)	Total c.p.m. $\gamma + \beta$	Total c.p.m. α^A	Total c.p.m. α^{CS1}	Ratio $\alpha/\beta + \gamma$
1	^3H -leucine	5	10,446	5,181	56	0.50
	^3H -leucine	120	154,546	64,704	751	0.42
2	^3H -arginine	15	2,850	1,436	14	0.51

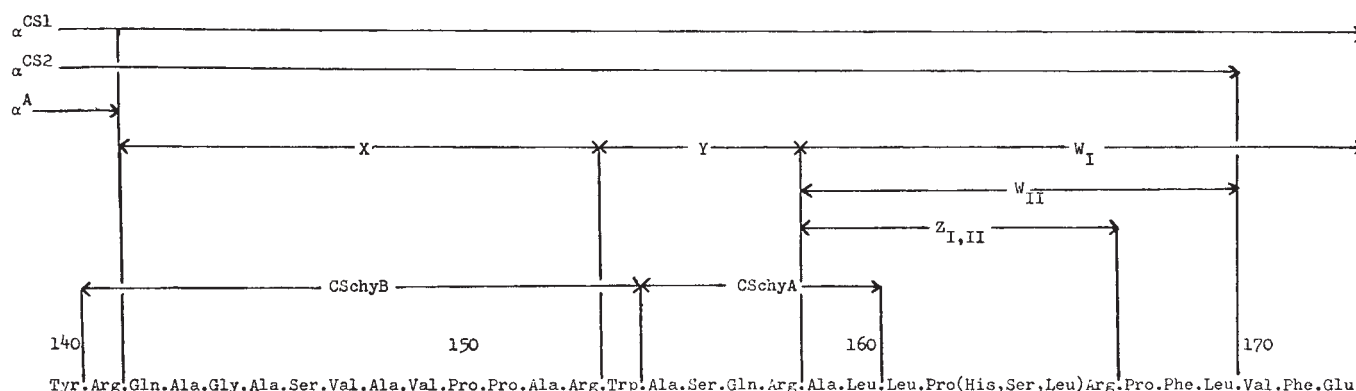
were incubated with ^3H -leucine for 1 h and haemoglobins H, A and CS separated by 'Amberlite' chromatography and the relative specific activities of the whole haemoglobins and their constituent globin chains determined. In the haemoglobin A fraction the specific activity of the α -chain exceeded that of the β -chain, indicating that there is a large pool of β -chains in these red cells and that newly made α -chains combine with β -chains from this pool. This too is typical of haemoglobin H disease⁶.

In all these experiments very little radioactivity was incorporated into the α^{CS1} and α^{CS2} -chains and their specific activities were considerably less than that of the α^A -chain.

however, since there is no significant difference between the specific activities of the N-terminal and C-terminal arginine-containing peptides of the α^{CS} -chain after 15 min of incubation with ^3H -arginine. If a reduced rate of assembly were responsible for a twenty-fold reduction in the rate of α^{CS} -chain production, compared with that of the α^A -chain, it seems unlikely that it would have been uniformly labelled after only 15 min, since it takes about 9 min at 37° C to uniformly label normal α^A -chains¹⁵.

The ratio of α to β -chain production in the parent heterozygous for Hb CS alone was 1.05/1, indicating no gross imbalance of globin chain production. This finding is similar to that reported for α -thalassaemia 2 carriers¹⁶. The α/β ratio in the other parent, heterozygous for α -thalassaemia 1, was 0.56, very similar to that reported for α -thalassaemia 1 heterozygotes¹⁶.

The structural and biosynthetic data indicate that Hb CS is a variant with an elongated α -chain and that as the red cell matures the ability to produce α^{CS} -chains declines more rapidly than the ability to produce α^A -chains. Furthermore, the associated genetic findings⁹ suggest that the *Hb CS* gene interacts with an α -thalassaemia 1 gene to produce haemoglobin H disease. In this respect the *Hb CS* gene behaves like the α -thalassaemia 2 gene, since Hb H is not normally found in the blood

**Fig. 2** Amino-acid sequences of the α^{CS1} and α^{CS2} -chains, showing some of the peptides isolated and used in the sequence determination. Full details of the determination of the sequences of α^{CS1} and α^{CS2} will be published elsewhere.

These observations, consistent for incubation times of 5 min to 2 h, indicate that the α^{CS} -chain has a low turnover rate and is not destroyed rapidly after synthesis. This was confirmed by determining the specific activities of the arginine-containing peptides of the α^A and α^{CS} -chains after incubating the cells of an individual heterozygous for α -thalassaemia 1 and Hb CS with ^3H -arginine for 15 min (Table 2). The lower specific activity of the α^{CS} -chain compared with α^A -chain suggests that either the ability to synthesize the α^{CS} -chain diminishes as the red cell matures, rather like the δ -chain of Hb A₂ (ref. 14), or that it is assembled more slowly than the α^A -chain. The data shown in Table 2 are not compatible with the latter possibility,

of individuals heterozygous for either the α -thalassaemia 1 or α -thalassaemia 2 genes alone, but only in persons doubly heterozygous for α -thalassaemia 1 and α -thalassaemia 2.

The Molecular Defect

There are several possible explanations for these observations. The simplest is that α^{CS} has arisen from a mutation of an α -chain gene terminating codon (UAA or UAG) to a glutamine codon (CAA or CAG) by a single base mutation or possibly by a deletion of the entire codon. This presupposes that the α -chain messenger RNA is longer than required to code for the 141 amino-acids normally present in the α^A -chain, and that in the absence of the normal terminating codon the message is read until another terminating codon is reached, so producing an α -chain with thirty-one extra residues attached to the C-terminal end. It is not clear from this model why this variant should be produced in such small amounts but it is unlikely to be due to a reduced rate of translation or termination of the additional piece of messenger RNA: the data on the rate of uniform labelling of the α^{CS} -chain are not consistent with this explanation. The production of small amounts of Hb CS could be explained by a terminating codon mutation if one assumes that the mutation is in a minor α -chain locus which normally directs the synthesis of about 1% of the total α -chain. Evidence for such a locus has been obtained in the great apes¹⁷. However, this mechanism would not explain the overall deficit

Table 2 Specific Activities of α^{CS1} -Chain Peptides and α^A -Chain Peptides after Incubation of Reticulocytes from an Individual heterozygous for α -Thalassaemia 1 and Hb CS for 15 min at 37° C

Peptide	Specific activity (c.p.m. ^3H -Arg/ μmol ^{12}C -Arg)
α^A 4	1,810
α^A 10	2,020
α^A 14	1,880
α^{CS1} 4	304
α^{CS1} 10	366
α^{CS1} 14	360
α^{CS1} X	283
α^{CS1} Y	279

of normal α^A -chains which accompanies Hb CS. Another explanation is that there is no further terminating codon after the normal termination point in the α -chain mRNA and that the small amounts produced result from a "pile up" of α^{CS} -chains which are released slowly from the ribosomes by non-specific proteolysis rather than by the normal process of chain termination. Again the data on the chain assembly time are not consistent with this model. Thus although a mutation in a chain terminating codon is perhaps the most likely, and attractive, explanation for the existence of Hb CS, it does not readily account for the small amounts produced or its relatively low rate of production in reticulocytes.

There are, of course, other possible explanations for the production of Hb CS, although none of them adequately explain both the small amounts produced and the relatively reduced rate of production in reticulocytes. Suppressor mutations have not been reported in mammalian cells but there is no reason why they should not exist.

A low efficiency suppressor of chain termination could explain the formation of small amounts of Hb CS although perhaps not its reduced rate of synthesis. A mutation in a minor glutamine transfer RNA, enabling it to recognize the chain terminating codon and insert glutamine, could account for the elongated α^{CS} -chain. A general suppressor of this type would be expected to suppress all appropriate chain terminating codons in other messenger RNAs. In most cases 1% of gene product would be undetected and even in the case of haemoglobin, which makes up 95% of the total protein in the red cell, only the fortuitous occurrence of charged residues in the extra piece enables the small quantities of Hb CS to be distinguished from haemoglobin A. We have no evidence of abnormal β -chains in these cells, but 1% of a β -chain variant with the same electrophoretic properties as Hb A would be very difficult to identify.

Finally, it is possible that the extra residues at the end of the α^{CS} -chain have arisen by unequal crossing over in a similar way to the Lepore haemoglobins, although the extra piece bears no resemblance to any other human globin chain. Possibly the cross over could have occurred with another gene altogether or with a globin chain gene which is out of phase as a result of the abnormal cross over. It has been suggested that thalassaemia-like disorders could result from crossing over between minor α -chain loci of the kind found in the great apes and the major α -chain loci¹⁷, but the length and composition of the extra piece make such a mechanism an unlikely basis for the production of Hb CS.

Recently another human haemoglobin variant with an elongated chain, in this case the β -chain, has been described¹⁸. In this variant the structure of the extra piece is not compatible with a termination codon mutation suggesting that such variants can indeed arise by a variety of mechanisms.

Whatever the explanation for the production of the small amounts of the elongated α^{CS} -chain it seems likely that the messenger RNA for normal α^A -chains is longer than that required to code simply for 141 amino-acid residues. This would agree with the recent finding that the molecular weight of rabbit haemoglobin messenger RNA, as determined by SDS-gel electrophoresis and ultracentrifugation, appears to be some 50% greater than that required for an RNA of sufficient length to code for the sequence of the α and β -chains alone^{19,20}. Our results suggest that haemoglobin α -chain messenger RNA has additional genetic material which extends for almost 100 nucleotides beyond the normal chain terminating codon.

Genetics and Distribution

The structure of Hb CS also has important implications for the understanding of the genetic control of the α -chain of human haemoglobin. There is conflicting evidence as to whether there are one or more structural loci directing α -chain synthesis, and, indeed, the situation may differ between populations^{21,22}. There is now good evidence that the α -thalassaemia 1 gene is associated with a total deficiency of α -chain production directed by the affected chromosome⁸. The

three individuals heterozygous for both α -thalassaemia 1 and Hb CS have haemoglobins A, H and CS. Thus the synthesis of both α^A and α^{CS} -chains must be directed by one chromosome and, unless the suppressor hypothesis is correct, this means that there are multiple α -chain loci on each chromosome, at least in the Chinese population in Jamaica. Furthermore, the similar mode of expression of the Hb CS and the α -thalassaemia 2 genes lends support to the suggestion that the α -thalassaemias are caused by total suppression of the α -chain production at either one (in the case of α -thalassaemia 2) or both genes (in the case of α -thalassaemia 1), of a duplicate α -chain-gene complex²³.

There have been reports in the past three years, from both Greece²⁴ and Thailand²⁵, of a minor haemoglobin variant being found in association with haemoglobin H disease. The Thai variant has an abnormal α -chain and its electrophoretic properties are very similar to Hb CS²⁵. Furthermore, recent observations in Hong Kong and Malaya (Drs Lie-Injo Luan Eng and D. Todd, personal communications) suggest that a haemoglobin similar to Hb CS is frequently observed in patients with haemoglobin H disease. It appears therefore that these Hb CS-like variants often occur in association with haemoglobin H disease and it seems unlikely that this is coincidental. A more probable explanation is that the α^{CS} gene complex behaves very much like an α -thalassaemia 2 locus, and is thus subjected to selection factors similar to those which have been responsible for maintaining the α -thalassaemia genes at a high level in these populations.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Black Holes and Binary Stars

Gibbons and Hawking¹ have suggested that a number of spectroscopic binaries contain black holes. The formation of a black hole in a binary system would be accompanied by a sudden loss of mass from the system, and they believe that this mass loss could convert an initially circular orbit into an appreciably elliptical one. Only masses greater than $1.4 M_{\odot}$ can collapse into black holes, and normal double-line spectroscopic binaries cannot contain black holes, so Gibbons and Hawking investigate those single-line spectroscopic binaries listed in the *Sixth Catalogue*² for which they estimate that each component has a mass greater than $1.4 M_{\odot}$. There are only seven such systems, three of which have orbital eccentricities greater than 0.08. On the other hand, there are 55 double-line systems in which both components are more massive than $1.4 M_{\odot}$, and eight of these have orbital eccentricities greater than 0.08. Comparing the relative numbers of eccentric and circular orbits in these two rather small samples, Gibbons and Hawking conclude that there is an excessive number of eccentric orbits among single-line spectroscopic binaries, and that the formation of black holes in some of the systems may have produced this excess. Specifically, they suggest that HD 176318, HD 184035 (201 G Sgr), and HD 194495 may contain black holes.

There are two implicit assumptions in this argument that, in our opinion, are not justified. The first is that the true frequency distribution of orbital eccentricities is similar to their observed distribution, and the second is that the observed frequency distribution of orbital eccentricities is expected to be the same for single-line and double-line spectroscopic binaries. There are three reasons for questioning their assumptions. (1) An orbit that is in fact circular may appear to have a small eccentricity introduced in the process of calculation of orbital elements by a fortuitous distribution of observational errors. (2) Some spectroscopic binaries that are also eclipsing binaries have velocity curves from which appreciable orbital eccentricities would be deduced were it not that the light curves clearly show these eccentricities to be spurious. Most of these systems are single-line binaries. (3) The probability of discovery of a spectroscopic binary depends on the orbital elements, in particular the eccentricity. Selection effects resulting from this dependence are strong enough to modify appreciably the observed distribution of eccentricities, and they act differently for single-line and double-line spectroscopic binaries.

Although Gibbons and Hawking restrict their discussion to orbital eccentricities greater than 0.08, the orbital eccentricity of HD 184035 is only 0.09. The period of this system is uncertain because only a few cycles have been observed³ and therefore the other orbital elements are probably more uncertain than is usual. The eccentricity, in particular, may be of the spurious kind defined in (1). Lucy and Sweeney⁴ have recently re-computed the elements of several spectroscopic binaries and tried to set up a test of the reality of small eccentricities. For HD 184035 they find $e = 0.049$ and judge that the orbit is essentially circular. Their result at least makes it doubtful whether the orbital eccentricity is large enough to suggest that

there is anything unusual about the invisible component.

The distortion of velocity curves mentioned in (2), was frequently commented on by Struve⁵. He pointed out that there is an excessive proportion of observed values of the longitude of periastron, ω , in the interval 0° to 90° . Savedoff⁶ showed that the values of $e \cos \omega$ obtained from light curves and velocity curves of the same eclipsing systems frequently differ—especially for binaries with periods less than 5 days that contain primary components of spectral type A5 or earlier. The detailed distribution of ω has been discussed most recently by Batten and Ovenden⁷. The distortion is often most pronounced in the Algol-type systems which contain a primary component of spectral type late B and a G-type or K-type sub-giant with a spectrum which is usually invisible except during the eclipse of the brighter star. For example, “eccentricities” of up to 0.5 and values of ω of about 45° have been found from velocity curves of U Cephei, although its light curve shows that $e \cos \omega$ must be close to zero. If a system of this type were not eclipsing, its secondary spectrum could not be detected. The distortion of the velocity curve is usually ascribed to phenomena within the orbital plane, but an Algol-type system that is oriented so as just to fail to display eclipses to a terrestrial observer may still have an appreciably distorted velocity curve. The periods, velocity ranges, and spectra of HD 176318 and HD 194495 are all consistent with the hypothesis that these systems are of this type.

Selection effects, mentioned in (3), are different for single-line and double-line binaries because a single-line binary is discovered by the variation of its velocity but a double-line binary is detected if its component spectra can be resolved. The probability of discovery depends on the elements e and ω , and on the orbital period, P . In addition, the discovery of a single-line binary depends on the ratio of the half-range of velocity, K , to the minimum detectable velocity variation Δ , while that of a double-line binary depends on the ratio of the sum of the half-ranges of each component, $K_1 + K_2$, to the minimum line separation, Δ' , needed to resolve the spectra. An extensive, unpublished investigation by Ovenden and Olowin shows that over a wide range of values of K/Δ or $(K_1 + K_2)/\Delta'$, the discovery probability of double-line binaries decreases more rapidly with increasing orbital eccentricity than does that of single-line binaries. This selection effect therefore acts in the right sense to account for the different proportions of eccentric orbits, discovered by Gibbons and Hawking, among the two kinds of binaries. Although its total effect in a large sample should not be large, it might well affect small samples such as they discussed. Scott⁸ has also studied the observed distribution of eccentricities on the basis of the catalogue compiled by Moore and Neubauer⁹. She calculated the observed distributions that would be produced by observational selection acting on a variety of assumed “true” distributions. When K/Δ is small, close to 2, none of the calculated distributions differ significantly from the observed distribution.

We are puzzled by the suggestion that image intensifiers be used in an attempt to detect the secondary components of HD 176318 and HD 194495. If each of these secondaries is about three magnitudes fainter than its respective primary, any spectrogram, no matter how it is made, will register pre-

dominantly the light of the primary star. We agree that observations in a different spectral region are desirable, especially, perhaps, in the red and infrared regions where the light of a normal secondary component would be relatively stronger.

Gibbons and Hawking find an apparent secondary maximum in the frequency distribution of e for double-line binaries that seems to us interesting. In view of the selection effects discussed above, this secondary maximum must correspond to a real effect in the velocity curves, provided that it is statistically significant, which, of course, is doubtful in so small a sample. Because seven of the eight systems that form this maximum contain stars of early B spectral types (for which the concentration of circular orbits should be greater because Δ and Δ' are large for stars of this type) the most likely explanation appears to us to be that these velocity curves are distorted in a way analogous to that in which velocity curves of Algol-type systems are distorted.

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Drs Hawking and Gibbons write: The two main points that Batten and Olowin make about our paper are:

1. The measured eccentricities of short period binaries are unreliable and may not represent real eccentricities.
2. There may be a selection effect which makes the detection of higher eccentricities more likely in single-line binaries than in double-line binaries.

We must agree with the first point. Since our letter was published there has appeared a recomputation of 201 G Sgr (HD 184035), which was one of the single-line binaries which we suggested might contain a black hole in view of its reported eccentricity of 0.09. The new computation of Lucy and Sweeney¹, however, lowers this value to 0.049. If this is correct it seriously weakens our argument, because it reduces the number of single-line binaries in our sample with "high" eccentricities from 3 to 2 whereas one would expect 1 on average, if the distribution of eccentricities for single-line binaries were the same as that for double-line binaries (but see Gott², succeeding communication).

Although measured eccentricities may be rather unreliable, we do not see any obvious reason why these should favour single line rather than double-line binaries. The selection effect mentioned by Batten and Olowin would appear to us to be small—indeed they admit as much when they say "its total effect in a large sample should not be large". Surely a selection effect which has a small effect in a large sample will have a small effect in any sample. The possibility of statistical fluctuations in a small sample is a separate problem.

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Further Evidence for Collapsed Objects in Binary Star Systems

It would be of great interest to discover a collapsed object (neutron star or black hole) as one component of a binary star system. Trimble and Thorne¹ have compiled a list of fifty candidate systems from Batten's² catalogue. These are non-eclipsing single-line spectroscopic binaries in which the unseen companion has a mass estimated to be greater than $1.4 M_{\odot}$. These unseen companions are thus too massive to be non-rotating white dwarfs (although the possibility that they are rapidly, differentially rotating white dwarfs cannot be completely excluded as Ostriker and Bodenheimer³ have shown). In principle, some of these unseen companions could be neutron stars or black holes. In most cases, including all those to be considered here, the unseen companion is less massive than the observed primary star and can be a normal main-sequence star, which is not observed simply because it is considerably less luminous than the primary. Recently, however, Gibbons and Hawking⁴ have presented evidence that suggests that one or more of the systems on the Trimble and Thorne list contain collapsed objects. Their argument is as follows. Let the initial binary system consist of two stars with masses M_1 and M_2 . Let the more evolved star (M_1) eject some of its mass and collapse to form a neutron star or black hole with gravitational mass M_{N1} . The ejected mass-energy can be in the form of a shell of matter or gravitational radiation, for example. If the initial orbit is circular and the mass loss can be treated as instantaneous and spherically symmetric, then the resultant binary system (M_2 , M_{N1}) will have an orbital eccentricity given by

$$e = \frac{M_1 - M_{N1}}{M_2 + M_{N1}} \quad (1)$$

(Note: the notation for the star masses above is not the usual notation for spectroscopic binaries.) Three of the seven systems from the Trimble and Thorne list with $P < 5$ days were found to have $e > 0.08$. By a comparison with short-period double-line binaries Gibbons and Hawking concluded that the probability of this occurring by chance is only 8%. This suggests that in one or more of the three systems, the eccentricity arises from a sudden mass loss and that the unseen companion is a collapsed object rather than a main-sequence star.

Table 1 Single-line Binaries from the Trimble and Thorne List with $P < 5$ Days, $e < 0.13$

Star	Spectral type	Aproximate distance	Period (days)	e	Corrected radial velocity V_R (km s ⁻¹)	$ V_R < \sqrt{V^2}^{\frac{1}{2}}$
HD 40005	B3V	430 pc	3.306	(0.037)	+5	0.5
201 G Sgr	A3III	140 pc	4.625	(0.049)	+18	1.2
HD 191473	B0.5V	1,500 pc	4.2876	0.070	+2	0.2
HD 198784	B3	440 pc	3.30353	(0.024)	+10	1.1
HD 209961	B2V	460 pc	2.1721	(0.0)	-3	0.3

These results must be revised somewhat in light of the recent work by Lucy and Sweeney⁵ which indicates that the originally quoted value of $e = 0.9$ for 201 G Sgr was entirely the result of observational error. Tables 1 and 2 tabulate the relevant data for the 7 binaries with $P < 5$ days from the Trimble and Thorne list. Eccentricity data are taken from Lucy and Sweeney whenever possible. A value in parentheses indicates that a circular orbit is compatible with the observational data. We note that the data for HD 176318 and HD 194495 are sufficiently accurate to assure that these are in fact high eccentricity systems. Following the procedure of Gibbons and Hawking, we select for comparison double-line binaries with $P < 5$ days, with both components $> 1.4 M_{\odot}$, with observational quality a to d in Batten's system, and for which the eccentricity was not assumed to be zero. We likewise exclude

Table 2 Single-line Binaries from the Trimble and Thorne List with $P < 5$ days, $e > 0.13$

Star	Spectral type	Approximate distance	Period (days)	e	K_1 (km s ⁻¹)	$\frac{M_2}{M_\odot}$	$\frac{\bar{M}_{N1}}{M_\odot}$	Corrected radial velocity V_R (km s ⁻¹)	$\frac{ V_R }{\langle V_R^2 \rangle^{1/2}}$	Predicted values $\frac{1}{2} \bar{V}_{sp}$ (km s ⁻¹)	$\frac{\bar{M}_1}{M_\odot}$
HD 176318	B6V	190 pc	2.912225	0.169	79.3	4.5	2.2	-13	1.4	16	3.3
HD 194495	B7	300 pc	4.9052	0.133	82.2	4.0	2.7	+24	2.4	9.5	3.6

γ Andr B from consideration. Of the 48 double-line binaries satisfying the above criteria only 5 have $e > 0.13$. On this basis, the probability that we would find 2 or more out of a sample of 7 with $e > 0.13$ is only 16%. Gibbons and Hawking's claim that the Trimble and Thorne list (with $P < 5$ days) contains an unusual number of high eccentricity systems is still quite valid.

We present here a test of the hypothesis of Gibbons and Hawking based on the fact that a high eccentricity is not the only consequence of a sudden mass loss. I have shown⁶ that a sudden mass loss from M_1 imparts a velocity V_{sp} to the resultant binary system (M_2, M_{N1}) and that V_{sp} is given by

$$V_{sp} = e \frac{M_2}{M_{N1}} \frac{K_1}{\sin i} \quad (2)$$

where K_1 is the observed radial velocity semi-amplitude of the star M_2 and i is the inclination of the orbit with respect to the line of sight. The resultant system (M_2, M_{N1}) is left with this additional velocity because its momentum must balance the net momentum carried away by the ejected matter. If mass loss is indeed responsible for the high eccentricities of the two systems in question we would expect these systems to show higher than average velocities as well. Because they are all spectroscopic binaries for which velocity curves have been obtained, the mean radial velocities of all the systems have been accurately determined. The distance to each binary was estimated by comparing the observed visual magnitude with absolute magnitudes as a function of spectral type as given by Cox and Guili⁷. An absorption coefficient of 1.0 mag kpc⁻¹ was used and stars were assumed to be on the main-sequence if no luminosity class was known. The observed mean radial velocities could then be corrected for differential galactic rotation as well as for the solar motion. The corrected radial velocities (V_R) are displayed in the tables and are compared with the r.m.s. corrected radial velocity ($\langle V_R^2 \rangle^{1/2}$) expected for a star of corresponding spectral type and position in the sky. For systems with spectral types B0–B5, the velocity ellipsoid for B0 stars is used to compute $\langle V_R^2 \rangle^{1/2}$ while for systems with spectral types B6–A3 the velocity ellipsoid for A0 stars was used. The velocity ellipsoid data were taken from Delhaye⁸. Since HD 40005 is a member of the I Orion Association, V_R for this system is taken to be its radial velocity with respect to the stars in the Trapezium. The distribution of $V_R/\langle V_R^2 \rangle^{1/2}$ for a random sample of stars is gaussian with a standard deviation of 1.0. The probability that a random sample of 5 stars would produce a larger value of $\chi^2 = \sum V_R^2 / \langle V_R^2 \rangle$ than that shown by the 5 binaries in Table 1 is 70%. Thus, these binaries possess lower than average velocities. By contrast, the two high eccentricity systems ($e > 0.13$) show abnormally high velocities as a group. The probability that a random sample of two stars would produce a larger value of $\chi^2 = \sum V_R^2 / \langle V_R^2 \rangle$ than that shown by the two binaries in Table 2 is only 2%. For the three systems, $\frac{1}{2} \bar{V}_{sp}$, the median value of the radial component of the imparted velocity due to mass loss is computed from equation (2). The mass of the observed star (M_2) is estimated from its spectral type and the mass of the unseen companion (M_{N1}) is estimated from the observed mass function $f(M) = M_{N1}^3 \sin^3 i / (M_{N1} + M_2)^2$. Throughout we take $\sin i = \sqrt{3}/2$ (its median value). The

values of $\frac{1}{2} \bar{V}_{sp}$, M_2 and $\bar{M}_{N1}$ as well as $\bar{M}_1$, the mass of the evolved star just prior to mass ejection, are tabulated for each system in Table 2. It is clear that the predicted values of $\frac{1}{2} \bar{V}_{sp}$ are of the right order of magnitude to explain the large radial velocities found for the two systems. The fact that the two high eccentricity systems show abnormally high velocities as a group and that these can be explained by the sample mass loss theory strongly supports the tentative conclusion of Gibbons and Hawking that one or more of these systems has suffered mass loss and that the unseen companion is not a normal main-sequence star.

For both HD 176318 and HD 194495 the mass of the more evolved star ($\bar{M}_1$) is found to be less than the mass of the less evolved star (M_2). This is a situation we could expect to find in such close binary systems. M_1 begins as the more massive star and evolves more rapidly. As it becomes a red giant it expands beyond its Roche lobe and begins to deposit matter on the star M_2 . Eventually M_1 is expected to become the less massive of two stars. This mass exchange process in close binaries is discussed in detail by Plavec⁹. In some cases such a process can leave the star M_2 with observable abundance anomalies. If abundance anomalies traceable to mass exchange can be found in the spectra of HD 176318 or HD 194495 it would constitute strong additional evidence that the unseen companion is the more evolved star and thereby likely to be a neutron star or a black hole.

The unseen companion in HD 194495 is estimated to have a mass greater than $2.2 M_\odot$ ($\sin i = 1.0$). This is greater than the upper mass limit of $1.95 M_\odot$ found for non-rotating neutron stars by Hartle and Thorne¹⁰. The mass of the unseen companion in HD 176318 may be either above or below this limit depending on the value of $\sin i$. A separate study of single line binaries⁶ has revealed another promising candidate, HD 59543, which is not discussed here.

To summarize, there are an unusual number of high eccentricity systems on the Trimble and Thorne list (with $P < 5$ days). In the present study I find a strong correlation between high velocities and high eccentricities. This evidence supports the suggestion that one or both of the high eccentricity systems may harbour a neutron star or a black hole. These two systems merit further investigation.

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Past Wind Strength from Isotope Studies

In this communication we explore the possibility that isotope studies can give palaeoclimatological data in addition to the well known determinations of past temperatures¹⁻³. We consider that the temperature difference between the equatorial and polar regions (ΔT) largely determines the storminess of our weather, and we will show that this information is recorded in the $^{18}\text{O}/^{16}\text{O}$ and $^2\text{H}/^1\text{H}$ ratios of the ice in the Greenland and Antarctic ice caps.

As a parcel of air moves from low latitudes to progressively colder regions, the water which is precipitated in the form of rain or snow is enriched in ^{18}O (and ^2H) with respect to the remaining vapour^{4,5}. Thus the vapour in the parcel of air becomes steadily enriched in ^{16}O and ^1H as it moves to colder regions, and from the $^{18}\text{O}/^{16}\text{O}$ ratio of the precipitation at a particular point the temperature difference between that point and the equatorial region (ΔT) can be calculated. Exactly equivalent data are obtained from $^{18}\text{O}/^{16}\text{O}$ and from $^2\text{H}/^1\text{H}$ studies, so for simplicity only $^{18}\text{O}/^{16}\text{O}$ work is considered here.

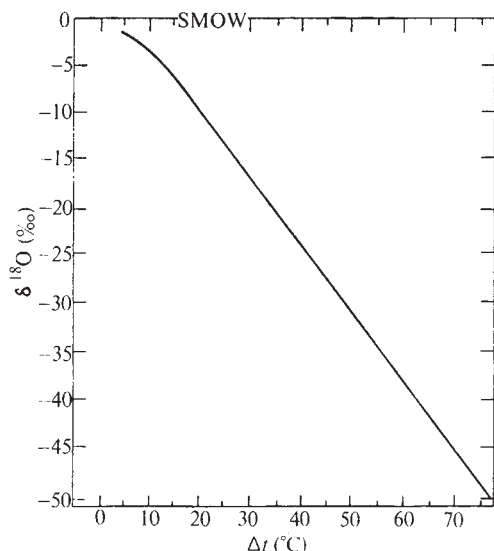


Fig. 1 Plot of temperature difference between the equatorial regions (25°C) and various points on the Earth versus depletion in ^{18}O of the precipitation measured in parts per thousand with respect to standard mean ocean water (SMOW). Data from Dansgaard⁵.

Using published data on the isotopic composition of present-day precipitation⁵, a plot of depletion of ^{18}O in precipitation at a given point against the temperature difference between that point and equatorial regions (ΔT) can be prepared (Fig. 1). The study of ΔT as a function of time for various regions of the Earth, using data from speleothems or water stored since glacial times in aquifers is an interesting problem in itself, but to obtain a measure of the past storminess of the Earth's weather requires the determination of (ΔT), the temperature difference between equatorial and polar regions. This information is now available in the form of $^{18}\text{O}/^{16}\text{O}$ profiles through the Greenland ice sheet at Camp Century (77°N)⁶, and $^{18}\text{O}/^{16}\text{O}$ and $^2\text{H}/^1\text{H}$ profiles through the Antarctic ice sheet

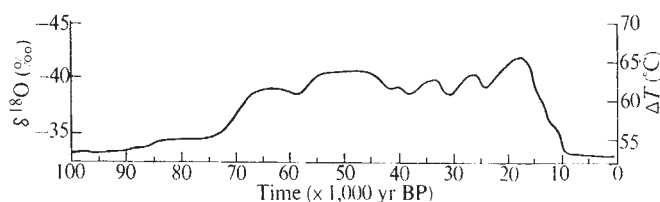


Fig. 2 Temperature difference between south polar region and tropics during past 100,000 yr. Data from Dansgaard⁵ and Epstein *et al.*^{7,8}.

at Byrd Station (80°S)^{7,8}. These data are presented in Figs. 2 and 3 as plots of the depletion of ^{18}O (with respect to standard mean ocean water, SMOW) in the precipitation versus time for Greenland and Antarctica. From Fig. 1 the data can be read as a plot of the variation of ΔT over the past 100,000 yr for both hemispheres. The most striking result is that during glacial periods the temperature difference between the equatorial and polar regions increased by 20 to 25%—in other words, glacial periods seem to be characterized by increased vigour of the wind circulation.

Strictly speaking, various corrections should be applied to the curves as follows: First, because neither ice core came from the centres of the respective ice sheets, the deeper parts of the cores contained snow which fell progressively further inland, with perhaps slightly different climatic conditions. From Figs. 2 and 3, however, we may see that the value of ΔT in the last interglacial is similar to that in the present interglacial, and, because this is a comparison between the top and the bottom of the core, any correction must be small. Second, the isotopic composition of the ocean changed due to the removal of water depleted in ^{18}O from the oceans to form the great ice sheets of the northern hemisphere during the Glacial Period. This is a very small effect, changing the world's oceans by no more than 1 to 2 parts per thousand, and would lead to an underestimate of the increase in ΔT during the Glacial Period. Third, the thickness of the ice sheets may change between glacial and interglacial periods. Briefly, because both the Greenland and Antarctic Ice Sheets are bounded by the sea, both now and in glacial times, the biggest effect is caused by the lowering of sea level which increases the area of the ice sheet⁹. This greatly increases the thickness on the margins of the ice sheet but has only a small effect in the central part of the sheet.

The isotopic data from the Greenland and Antarctic cores suggests that when the Earth cools, ΔT increases, that is, the polar regions cool more than the tropics. This is probably because cooling causes greater albedo changes at high latitude, attributable to increased ice and snow cover, and hence reduces the solar energy input. This might explain why the increase in ΔT for the northern hemisphere during the last glacial period was greater—25% (Fig. 3)—than for the southern hemisphere—20% (Fig. 4)—where most of the high latitude land is snow and ice covered even in interglacial times. On this model even the present weather would be a result of the fact that our polar regions have an increased albedo because of snow and ice cover. If the melting point of water were, say, 5° lower, our weather would be much more benign.

Fig. 4 is a generalized plot of how ΔT changes with temperature of the equatorial regions. An implication of this curve is that if the Earth were to warm, ΔT would decrease, that is,

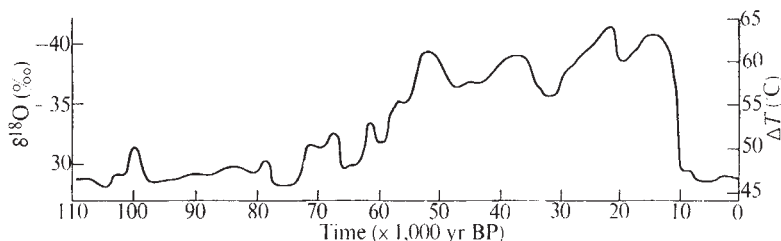


Fig. 3 Temperature difference between north polar region and tropics during past 100,000 yr. Data from Dansgaard⁵ and Dansgaard *et al.*⁶.

the polar regions would be warmed more than the tropics. This suggests that warmer periods in the past—say early Tertiary times—were periods of less wind and where the equator was only slightly warmer but the regions of higher latitude were much warmer. There is considerable plant fossil evidence to support at least the latter of these conclusions (see, for example, refs. 10 and 11).

If the glacial periods are in fact periods of much more violent weather, this should be recorded in the geological record. Glacial periods are normally associated with the formation of ventifacts and extensive loess deposits, derived from material supplied by glacial flood plains. Others, including the classic loess deposits in China, were far removed from any ice sheet and can probably only be explained in terms of greater windiness in the China/Gobi Desert area. Similar arguments can be advanced for the fossil sand dunes of central Australia. Australia was far removed from any ice sheet and is believed to have been wetter during the last glacial period. Yet large dune systems now dormant were probably active at that time. The only possible explanation seems to be that the glacial period in Central Australia was a period of significantly greater windiness than at present. In North America there is considerable evidence for greater windiness during the most recent and earlier glacial periods. For example, in the Sweetwater and North Platte drainage systems there was considerable deflation and dune formation during the last glacial period, whereas in post-glacial times the dunes have been stabilized and there is little wind erosion (G. Richmond, personal communication). Again, in central and western Nebraska dunes which were moving in glacial times are now stabilized¹².

As well as the very large temperature fluctuations (6°C) between glacial and interglacial periods, the Earth goes through small temperature fluctuations ($1.5^{\circ}\text{--}2^{\circ}\text{C}$) (see, for example, Lamb¹³). There was a very warm period in the twelfth and thirteenth centuries (so-called "Little Climatic Optimum") with a sharp decrease in the fourteenth century into the so-called "Little Ice Age" of the fifteenth, sixteenth, seventeenth, eighteenth and early nineteenth centuries. The Antarctic core has not been measured with sufficient detail, but the Greenland curve shows that even these smaller temperature fluctuations have increased ΔT . Fig. 5 has been calculated from Dansgaard's data⁶ and shows that the transition from the Little Climatic Optimum to the Little Ice Age involved an increase in ΔT of 1°C or about 2.5% with a consequent increase in storminess.

This sharp change in climate may have important implications in meteorology and history. For example, it may have

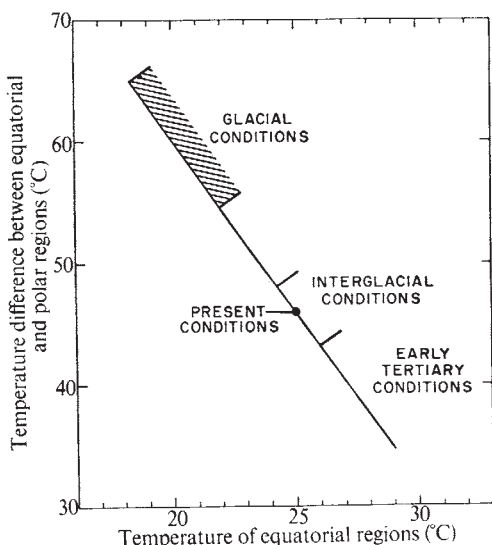


Fig. 4 Generalized plot of how ΔT changes with the temperature of the equatorial regions—for the northern hemisphere.

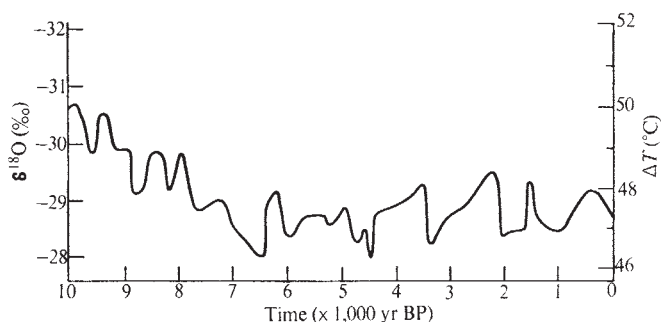


Fig. 5 Temperature difference between north polar region and tropics during past 10,000 years. Data from Dansgaard⁵ and Dansgaard *et al.*⁶.

been the increase in storminess that led the Vikings to abandon their North Atlantic route with the onset of a cold period rather than seek a more southern route. Similarly, the Polynesian migrations in the Pacific started with the onset of a warm period and ended at the onset of the Little Ice Age. It has always been difficult to understand how the Polynesians could have settled New Zealand from Tahiti by the early fourteenth century and then not have gone on to discover Tasmania and Australia. If the Little Climatic Optimum had been a period when very violent storms were rare, this would explain how the Polynesians could explore and settle the South Pacific in a few hundred years. If the break in climate in the eighteenth century caused a sharp increase in the frequency of violent storms, the loss of a relatively few skilled navigators could have effectively discouraged further exploration.

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Imaging the Rhodium Atom with a Conventional High Resolution Electron Microscope

THE ability of microscopes to make single atoms of metals visible has been reported by Muller¹ and more recently by Crewe *et al.*². Muller has been working with the direct imaging method of field-ion microscopy, which produces images of single atoms in the surface of solid specimens. Crewe used a high resolution scanning microscope developed in his laboratory

to image thorium and uranium atoms in an organic molecule. In neither case was a conventional electron microscope used.

Although resolutions of better than 0.2 nm (2 Å) have been reported with conventional transmission electron microscopes, little hope had been given that these instruments could be used to obtain the image of a single atom. The problem was one of lack of contrast between the heavy atoms and their support. Crewe overcame this contrast problem by using a special electron detector placed in a position which discriminated between the elastic and inelastic scattered electrons and measured primarily the elastically scattered electrons. In our investigation, we have been able to maximize the difference in the elastic scattering of electrons by light and heavy atoms through proper objective aperturing of a conventional transmission electron microscope and have observed for the first time individual rhodium atoms on silica.

Lenz³, in his study of the angular intensity distribution of electrons of intermediate energies (50–150 keV) scattered at very small angles, has shown that elastic scattering involves much larger scattering angles than does that for inelastic scattering. The angles of scattering resulting from the elastic scattering process are sufficiently large ($>10^{-3}$ radians) that they can be apertured out in the objective lens of an electron microscope, thereby improving contrast. This is the common practice. Lenz also calculated the ratio of the total elastic scattering cross section, σ_e/σ_i , for atoms of different atomic number. These data can be reduced to the empirical expression

$$\sigma_e/\sigma_i \sim Z/19-20$$

and is independent of the accelerating voltage of the electron beam. Our objective was to calculate, using Lenz data, the size aperture which, when used in the objective lens of our microscope, would minimize the removal of scattered electrons (inelastic) due to silica from the electron beam while maximizing the removal of electrons elastically scattered by the rhodium. For our microscope, a Philips EM-300 with high resolution objective pole pieces, this condition exists at 5×10^{-3} radians. For the position of the objective aperture in the EM-300, this angle corresponds to an aperture diameter of 30 μm . This size objective aperture was used for our studies of rhodium on silica.

Rhodium catalysts were prepared by impregnating a silica support with an aqueous solution of $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$. The

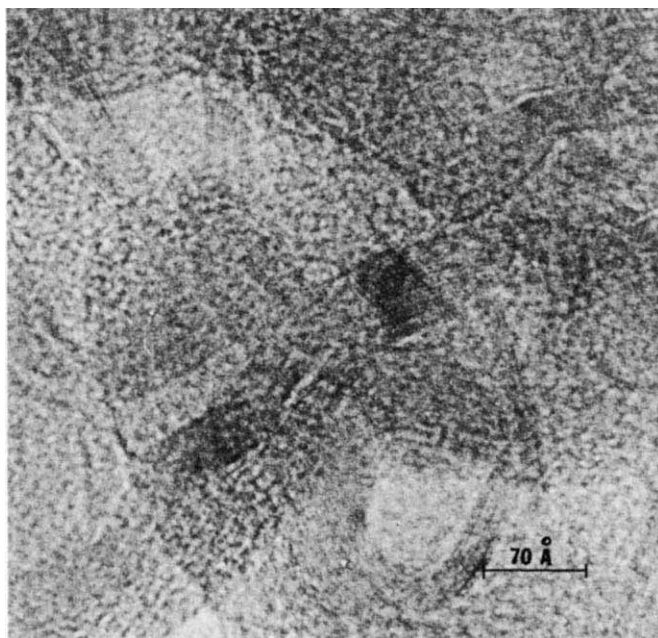


Fig. 1 Graphitized ISAF carbon black used as calibration specimen, $d_{002} = 0.344$ nm. A 30 μm aperture is in place in the objective lens.

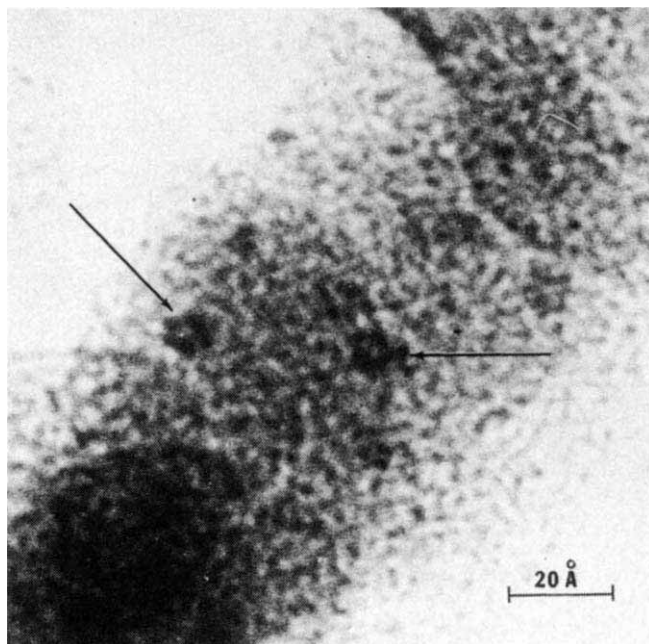


Fig. 2 Rhodium atoms on silica. Arrows indicate clusters of rhodium atoms. A 30 μm aperture is in place in the objective lens.

silica was 'Cabosil HSS' obtained from the Cabot Corp., Boston. The samples were reduced *in situ* in flowing hydrogen for 16 h at 400° C, the Rh concentration being 1.0 weight %. The degree of dispersion (or surface area) of the Rh after reduction was obtained by measurements of H_2 and CO chemisorption at room temperature. It was found that the Rh was very highly dispersed, with an average crystallite size of 1.2 nm (12 Å). Indeed, the Rh was atomically dispersed in the sense that every Rh atom in the sample was accessible to gas and either adsorbed one hydrogen atom or one CO molecule. The value of 12 Å was later confirmed by direct measurement using the electron microscope. Complete details of catalyst preparation and chemisorption are presented elsewhere⁴.

No modifications of the electron microscope were made, other than using a pointed filament (Ladd Research Industries) to provide a more coherent electron beam. The laboratory housing the microscope, however, has been specially constructed to reduce vibration to less than 2×10^{-6} inches s^{-1} and is shielded from stray magnetic fields. The area surrounding the specimen was cooled to -160°C to reduce contamination (<0.1 Å min^{-1}) and changes of astigmatism during operation of the microscope.

The catalyst sample was ground and ultrasonically dispersed in butyl alcohol with a small amount of partially graphitized ISAF carbon black and deposited on a "holey" carbon film. The ISAF carbon black was used as an internal magnification and resolution standard as suggested by others⁵. The micrograph of the black shown in Fig. 1 was taken with the 30 μm objective aperture in place. This shows the 0.344 nm (3.44 Å) 002 spacing and attests to image quality in the molecular size range. Contrast is lower than that obtained on the carbon black when the aperture is not used but is sufficient to allow instrument checks under exactly the same conditions as those used on the catalyst.

Fig. 2 is a micrograph of rhodium on silica using a 30 μm objective aperture. Clusters are visible that are probably rhodium atoms and are approximately 1 nm (10 Å) in diameter with the diameter of the individual spots in the cluster being 0.27 nm (2.7 Å) ± 0.02 nm. This value corresponds closely to the atomic diameter of rhodium given by Hume-Rothery and Raynor⁶ of 0.2690 nm. The spacings between the atoms measured from the micrograph are 0.35–0.40 nm. Again, this is in good agreement with the lattice spacing given for the face-

centred cubic structure given for rhodium of 0.3805 nm. Resolution of the clusters into individual atoms was obtained on successive micrographs of the same field and at $\pm 3^\circ$ tilt of the specimen about the axis of the electron beam.

We feel that these data, and micrographs obtained from other heavy metals, indicate that we have succeeded in obtaining images of isolated individual atoms using a conventional high resolution electron microscope. Data of this type can be of considerable help in obtaining the detailed structure of supported metal catalysts in respect to the clustering of the metal and the topographic details.

Note added in proof. The referee has pointed out to us that the principle of optimal sizing of the objective aperture for differential contrast had been previously suggested in a theoretical study by Cosslett (*Lab. Invest.*, **14**, 1009; 1965); we were not aware of this work when our calculations were made.

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Silver ^{108m}Ag Dating in Marine Organisms

WE have read with interest the recent letter by Beasley and Held¹ which voices reservations concerning the origins of the ^{108m}Ag and ^{110m}Ag reported by us². Their comments are well thought out and deserve a careful reply.

First, we did not mean to imply that the ^{108m}Ag and ^{110m}Ag observed in the Pacific marine organisms was actually produced primarily by thermal neutron activation of stable silver; only that the assumption of an initial $^{110m}\text{Ag}/^{108m}\text{Ag}$ activity ratio value of 162 yielded apparently reasonable dates of original production of the radiosilver falling within the 1961–1962 atmospheric nuclear weapons testing period. It is true that the value 162 came from a reactor experiment³ involving thermal and epithermal neutrons. But we first assumed it, not for this reason, but rather because it was then the only number available to us. We continued to use it because, rather remarkably, it gave reasonable results.

As Beasley and Held suggested, the reaction $^{109}\text{Ag}(n,2n)^{108m}\text{Ag}$ does seem to be important in thermonuclear bomb production of radiosilver. More recent measurements, which we have just concluded on a sizable number of marine organisms collected in 1964–1965, suggest that the radiosilver in those samples had a rather uniform initial $^{110m}\text{Ag}/^{108m}\text{Ag}$ activity ratio of about 180. We consider this last value to be the result of a combination of fast neutron capture on ^{109}Ag and on ^{107}Ag , which should produce an initial ratio of about 400, together with ^{108m}Ag production by the $^{109}\text{Ag}(n,2n)$ reaction.

Beasley and Held also cited measurements in the environment of radiosilver from pre-1959 nuclear weapons testing, and suggest that ^{108m}Ag left over from that period might be expected to affect the radioactive datings made by us on 1964–1965 marine biological samples. We have found one sample collected directly downstream from the US Pacific Proving Ground in 1964 which does seem to contain some pre-1959 ^{108m}Ag . In general, however, we believe that radiosilver from the latter period should have an insignificant effect on the $^{110m}\text{Ag}/^{108m}\text{Ag}$ datings of 1964–1965 samples, based on

(1) the fact that many more megatons of thermonuclear weapons were reported⁴ detonated in the atmosphere in 1961–1962 than pre-1959, (2) the effects of turnover in the environment between the two periods and (3) the nature of the dating formula.

Beasley and Held state in their letter that the (n,p) reactions on stable cadmium are probably not important as producers of ^{108m}Ag and ^{110m}Ag in thermonuclear explosions “because the quantity of stable cadmium in nuclear devices would probably be kept to a minimum on account of the large thermal neutron cross sections”. But it has been reported⁵ that there was one shot in the 1962 US Test Series into which cadmium was intentionally introduced to produce a tracer of ^{109}Cd , namely the “Starfish Prime” explosion of July 9, 1962, at an altitude of about 400 km over Johnston Island. The possible presence of 1964–1965 environmental samples of radiosilver from cadmium in this explosion must also be considered, as it is not immediately obvious that such production would have been insignificant in comparison with other production during the 1961–1962 testing period.

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BIOLOGICAL SCIENCES

Chromosome Analysis of Abnormal Cells

I REGRET to say there was an error in my recent communication “Chromosome Analysis of Abnormal Cells”¹. In Fig. 2 cell *a* is shown with only fifty-four chromosomes whereas cell *b* has

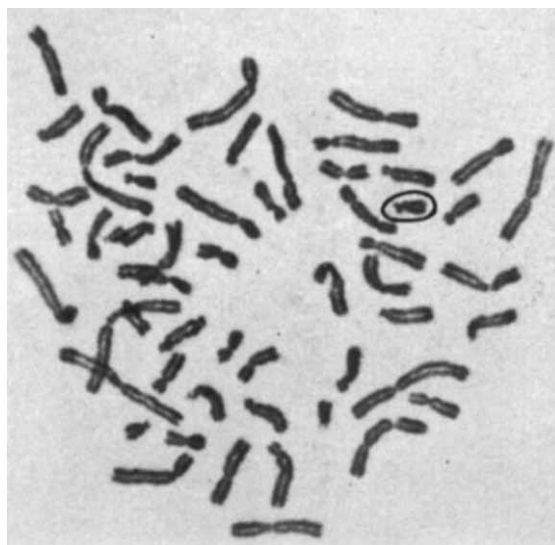


Fig. 1

fifty-five chromosomes. In preparing Fig. 2a one chromosome was unfortunately omitted although it was included in Fig. 3, the correct interpretation of the two cells. The chromosome in question is ringed on Fig. 1 here and would have been placed in group G of the Denver-London system.

Although this error is most regrettable, it does not in any way alter or invalidate the argument put forward in my letter concerning the unsuitability of the Denver-London system for analysing highly abnormal chromosome constitutions.

I thank Professor P. C. Koller for bringing this mistake to my attention.

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Received June 29, 1971.

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Variant of the Fluorescence Pattern in an Abnormal Human Y Chromosome

WILSON *et al.*¹ and Morillo-Cucci and German² have reported on large Y chromosomes with a terminal non-fluorescent segment of the long arms. We have found another variant of the fluorescence pattern in a large Y.

Our subject was a 36 yr old healthy man of normal body proportions, whose chromosomes were analysed because his first child, a female, had died with the clinical diagnosis of the trisomy 13 syndrome. His son, who is 4 yr old now and clinically healthy, has the same variant Y chromosome as the father: the Y chromosome was consistently as large as the D group chromosomes. No prominent constriction was seen in orcein-stained preparations, although some fuzziness could be demonstrated along the whole length of the long arms, as described for normal Y chromosomes. Quinacrine dihydrochloride fluorescence staining of blood cultures showed a non-fluorescing gap at about the midpoint of the strongly fluorescing portion of the long Y arm. This gap was consistently found in all metaphases examined (Fig. 1). The consistency of this finding in all metaphases regardless of chromosome contraction differentiates this constriction from the occasionally occurring less fluorescing gap of normal-sized Ys.

The explanations put forward by Wilson and coworkers¹ also apply to our cases. Either the fluorescence patterns of

long Y chromosomes show variants of different kinds, or this case and other cases of abnormal Y chromosomes represent examples of structural rearrangement. Morillo-Cucci and German² assumed a duplication of a portion of the long Y arm in their case. In our case a duplication of Y long arm material including a small part of the non-fluorescing portion, or, less probably, an insertion of autosomal or X chromosome material into the intensely fluorescing part of the long Y chromosome, would be possible explanations.

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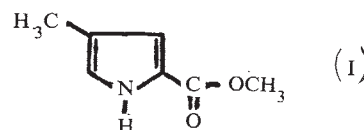
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Identification of the Trail Pheromone of a Leaf-cutting Ant, *Atta texana*

THERE are numerous reports of the isolation and identification of insect sex pheromones, and recently a termite trail-following pheromone was isolated and identified¹, but this is the first isolation and identification of an ant trail pheromone to be reported. We have identified the major volatile component of the trail marking substance laid down by the town ant, *Atta texana* (Buckley), as methyl 4-methylpyrrole-2-carboxylate (I). The worker ants of *Atta texana*, whose trail marking substance contains both volatile and nonvolatile components², readily followed trails made by us with synthesized (I).



The whole bodies of 3.7 kg of worker ants of mixed sizes obtained from Grant Parish, Louisiana, were macerated in methylene chloride and the soluble material was distilled in a short-path still onto a condenser (cooled with dry ice) at 90°C and 0.05 mm Hg. The trail-following response³ of the minor workers from a laboratory colony was used to monitor this and all subsequent isolation steps. The active nonvolatile material was saved for future study, and the volatiles were used for this investigation. The active distillate was fractionated by gas chromatography. Successive vapour phase chromatography (VPC) of the major active component on four columns (SE-30, diethylene glycol succinate, Carbowax 20 M, and silicone DC QF-1) yielded 150 µg of a single compound. This very potent trail pheromone, when rechromatographed on the columns, gave a single symmetric peak on each column. Four other VPC fractions, which have not been purified or identified, are active at about ten times higher concentrations than the major active compound and are present in about five to twenty times smaller amounts.

On the basis of mass, infrared, and nuclear magnetic resonance spectra, we assigned structure (I) to the pheromone, which was confirmed by congruence of these data and of VPC retention times with those properties of an authentic synthetic sample⁴.

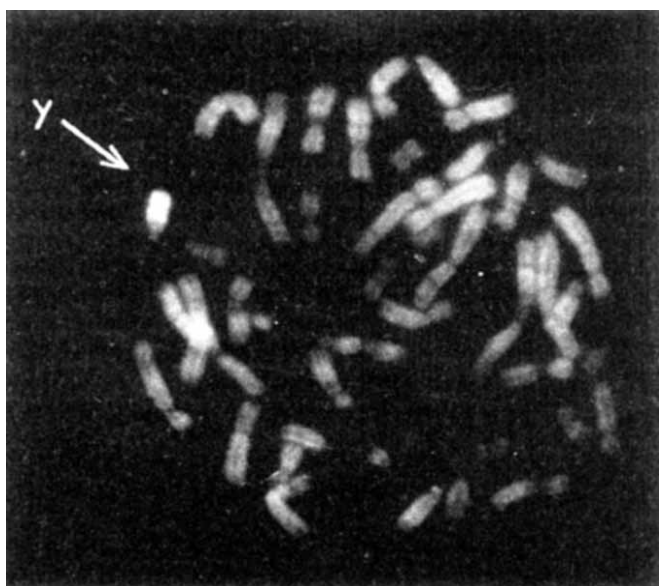


Fig. 1 Chromosomes showing the abnormal Y with a non-fluorescing gap.

Potency of the synthesized (I) was evaluated by describing on slick cardboard sheets, 50 cm circumference circles with serially diluted 10 μ l. chloroform solutions. Twelve minor workers from a laboratory colony were then released into the centre of the circle. The lower threshold of detection was 0.08 pg/cm (3.48×10^8 molecules/cm), about the same as that recorded for *R. virginicus*¹. Thus only 0.33 mg would be required to draw a detectable trail around the world. Strong responses were obtained from 0.8, 8.0, and 80.0 pg/cm, but 0.8 ng/cm produced some repellency. Minor workers were completely repelled by concentrations of 8.0 ng/cm and above. Volatility of the pheromone was demonstrated by placing the minor workers on plastic sheets 1 mm above the trail². Workers detected the odour at a concentration of 80 pg/cm and strongly responded at 0.8 ng/cm described on the trail below the plastic sheet.

Medium and large workers were then tested on natural trails leading from nests in the field. They readily followed a 2.7 pg/cm trail on a 15 cm strip of cardboard placed across an "erased" portion of the trail. They detected another trail made by dribbling 4.0 pg/ μ l. on the sand at a 45° angle to the field trail; response was strong at 40.0 pg/ μ l.

We thank Dr Henry Rapoport for 4-methylpyrrole-2-carboxylic acid. This work was supported by a US Public Health Service grant.

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Design and Synthesis of Controlled Release Pesticide-Polymer Combinations

ALTHOUGH the indiscriminate dissemination of pesticides into terrestrial and aquatic ecosystems is reprehensible, the magnitude of the pest control problem will necessitate the use of these materials for the foreseeable future. Persistent pesticides are undesirable because of their frequent incorporation into the food chain¹⁻³. On the other hand, pesticides with short lives tend to be ineffective. In both cases, the amounts applied are often grossly in excess of that actually required to control the pest because of the need to compensate for pesticide loss by leaching and evaporation. We have therefore investigated

the potential of pesticide-polymer combinations as a means of securing controlled release of a biodegradable pesticide in approximately the correct amount needed over an appropriate period of time.

The fundamentals of such controlled release systems are currently being investigated primarily for forestry applications such as the 5 yr suppression of competitive deciduous brush in the presence of conifers in the temperate Pacific North-West⁴⁻⁶ and in tropical Costa Rica⁷, the prevention of damaging attack on commercially valuable mahogany and Spanish cedar by the shoot-borer, *Hypsipyla grandella* Zeller. Two distinct approaches are now reported. (a) Pesticide release by diffusion through polymers, and (b) pesticide release by degradation of a polymer containing the pesticide as a pendent side chain.

For case (a) the active pesticide is dissolved or encapsulated in a polymeric matrix and the combination is placed in the medium where pesticidal activity is desired. Release occurs by diffusion so that no specific structural moiety within the pesticide molecule is necessary. The method therefore has general applicability for the controlled release of a wide variety of biologically active materials. Furthermore, a broad range of polymer matrices are also functional although it has now been found that molten polyamides or other polymers containing backbone amide linkages such as polyurethanes are especially versatile because of their remarkable solvent powers for pesticides in general⁵ and the fact that this solvency is maintained after cooling. Solid solutions of pesticide (>25% w/w) in polyamides (M_n , 2,000-15,000) synthesized from ethylenediamine and the dimer of linoleic acid can be routinely prepared. Using the housefly chemosterilant hexamethylphosphoric triamide (HMPT)⁸ as a water-soluble model for a typical systemic organophosphorus pesticide and polyamides (M_n , 15,000) from ethylenediamine and dimerized linoleic acid as the matrices, the release rates were determined for a series of cylindrical pesticide-polymer blocks (diameter 3 cm) by contacting only one circular face with vigorously stirred water (200 ml.). The HMPT released, determined by neutron activation analysis, varies with the square root of the elapsed time (Fig. 1) in accord with diffusion theory^{5,9}. The general solvency of amidic polymers coupled with computer evaluation of diffusion coefficients can therefore be used to design a wide range of controlled-release pesticide-polymer combinations the duration of whose effectiveness is adjustable. For case (b) the pesticides, exemplified by the herbicidal phenoxyacetic acids (RCOOH), are chemically attached as a pendent substituent to a natural or synthetic water-soluble or insoluble polymer

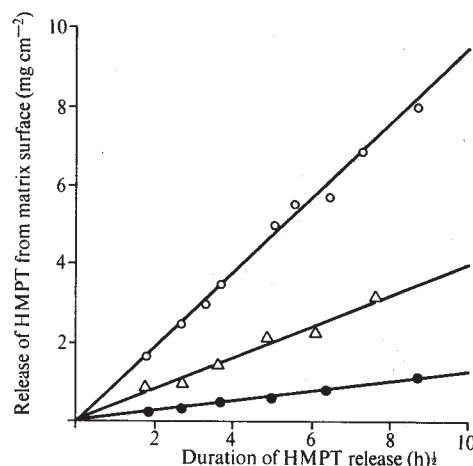


Fig. 1 Rate of release of hexamethylphosphoric triamide (HMPT) from a polyamide matrix. ○, 21.48% HMPT—polyamide solid solution; △, 14.00% HMPT—polyamide solid solution; ●, 6.90% HMPT—polyamide solid solution.

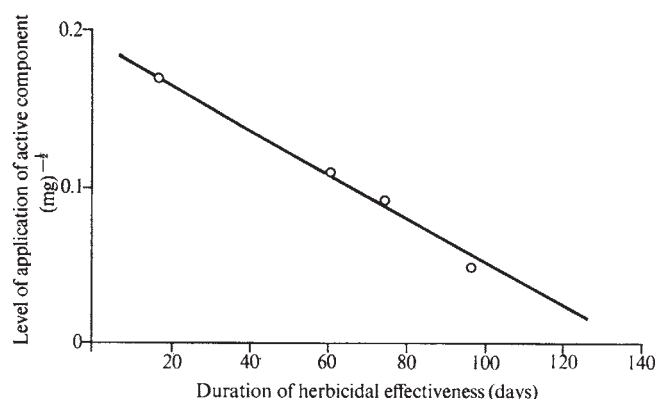
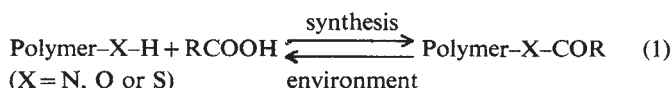


Fig. 2 Relationship of duration of herbicidal effectiveness to level of application for 2-methyl-4-chlorophenoxyacetic acid chemically combined with a water soluble polymer.

having a replaceable hydrogen as formulated in equation (1). Obviously the pesticide must also contain a structural moiety suitable for use as a link to the macromolecule¹⁰, and the carboxyl group is only one of the many alternatives possible.



Pesticide-polymer combinations of this type can readily be synthesized by, for example, conventional acylation of a solution (dioxan, pyridine) or suspension (benzene) of the backbone polymer using the acid chloride of the pesticide acid¹¹.

In the biological environment, side chain degradation occurs so that the chemical bonds holding the pesticide within its polymeric prison are sequentially broken to provide a sustained release of the pesticide over an extended period of time. The rate of release will clearly be determined by the nature of the pesticide-polymer bonds, the chemical characteristics of the pesticide and polymer and the dimensions and structure of the resultant macromolecular combination. Where the polymeric backbone is water-soluble the duration of pesticide release (D_{pr}) for n spherical particles (radius r and density ρ) of the pesticide-polymer combination in a water-saturated heterogeneous surface reaction is given by

$$D_{pr} = \rho r_o / k_h C_o - (R_h \rho^2 / n \pi k_h^3 C_o^3) \quad (2)$$

where C_o is the initial concentration of pesticide-polymer linkages on the surface of a particle of radius r_o , R_h is the rate of hydrolytic degradation and k_h is the hydrolysis rate constant. Since each pesticide molecule released by hydrolysis exposes another pesticide-polymer linkage beneath, C_o is a constant and the duration of pesticide release (D_{pr}) can be predicted from equation (3) in which

$$D_{pr} = A - B\sqrt{W} \quad (3)$$

where A and B are constants and W is the amount of pesticide-polymer combination used. The validity of this equation is demonstrated by the linear plot (Fig. 2) of the persistence of herbicidal activity⁵ exhibited by a polymer synthesized by the partial acylation (56.1%) of polyvinyl alcohol with 2-methyl-4-chlorophenoxyacetyl chloride. The duration of pesticide release was determined by observation of the inhibition by a herbicide of seed germination in lettuces sown daily. Equation (3) also defines the minimum amount of pesticide-polymer combination ($W = A^2/B^2$ when $D_{pr} = 0$) necessary for pesticidal activity.

On the other hand, the polymeric backbone selected may be water-insoluble and cellulose and lignin, the macromolecules of wood and bark, are particularly appropriate choices because of their long-established biodegradability and ecological acceptability and because of their abundance as low-cost solid wastes¹². Marine¹³ and proteinaceous¹⁴ solid wastes can also be used as the polymeric backbone. Acylation of these natural hydroxylated polymers¹⁵ with a pesticide acid chloride affords pesticide-polymer combinations which degrade by a heterogeneous surface reaction to provide a sustained release of pesticide.

The duration of effectiveness (D_{pr}) of this type of sustained release pesticide-polymer combination is given by

$$D_{pr} = (1/k_d)(\ln W - \ln R_d/k_d) \quad (4)$$

where W is again the amount of pesticide-polymer combination used, R_d is the rate of degradation and k_d is the degradation rate constant.

Since k_d and R_d are constants for a given system, equation (4) can be simplified so that

$$D_{pr} = M \log_{10} W - N \quad (5)$$

where M and N are constants. In this case the minimum amount of pesticide-polymer combination necessary for pesticide activity is $10^{N/M}$ ($D_{pr} = 0$). Experimental confirmation of the usefulness of equation (5) in the design of controlled release pesticide-polymer combinations is again provided by the lettuce seed germination bioassay of the release of herbicide acids⁴ from esters of cellulose and lignin (Fig. 3).

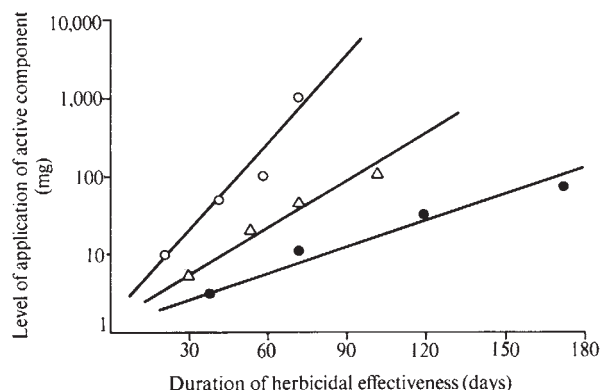


Fig. 3 Relationship of duration of herbicidal effectiveness to level of application for 2,4-dichlorophenoxyacetic acid (2,4-D) chemically combined with water insoluble polymers. $\circ$, 2,4-D alone; $\triangle$, 19.7% 2,4-D/Douglas fir bark chemical combination; $\bullet$, 39% 2,4-D/kraft lignin chemical combination.

The ecological implications of the results in Fig. 3 are particularly profound because the controlled release combinations in comparison with free pesticide provide either an extended period of protection at equivalent levels of application or the same period of protection at greatly reduced levels of application. Clearly, both of these alternatives tend to reduce the environmental hazards associated with the continued conventional use of pesticides. Although developed for forest pest control the systems described should be broadly applicable to the controlled release of other biologically active substances¹⁶.

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Contraction of Single Smooth Muscle Cells from *Bufo marinus* Stomach

MANY aspects of vertebrate smooth muscle function cannot be studied adequately in the whole animal or *in vitro* because the collagen net surrounding individual cells distorts force-time relationships¹. Electron microscopy of smooth muscle tissues has provided some data on structural changes during contraction^{2,3}, but the difficulty in obtaining sections in the correct plane and lack of a suitable method for viewing contractile elements in three dimensions has impeded progress. Lowy and Small⁴, using a weight to stretch guinea-pig taenia coli during fixation and dehydration, observed a ribbon-like arrangement of myosin filaments but could not study contracted cells prepared the same way.

A method for studying isolated smooth muscle cells would overcome many of the difficulties encountered with smooth muscle as a tissue. A technique for isolating living, beating heart cells using collagenase and trypsin has been developed by Vahouny *et al.*⁵, and we have modified it to isolate smooth muscle cells and determine whether they were intact and living.

Bufo marinus circular stomach muscle was used because this animal is relatively cheap, and available throughout the year from suppliers (Lemberger Co., Oshkosh, Wis.), and each specimen can provide a comparatively large amount of circular stomach muscle.

An adult *Bufo marinus* (200–300 g) was double-pithed and the stomach removed and stretched over a glass rod. Fine forceps were used to remove the serosa, and thin strips of the circular muscle were peeled away from the underlying mucosa and pinned to a cork board. Each strip was cut into 2–3 mm segments, and the pieces were placed in a test tube containing 2 ml. of solution A: 0.1% trypsin (Sigma, type III), 0.1%

collagenase (Sigma, type I), dissolved in Harris Ringer⁶ and maintained at 31° C.

After 1 h of incubation the supernatant was removed and replaced with 1 ml. of solution B which differed from solution A in having only 0.05% collagenase. At 30 min intervals thereafter, the supernatant was removed and replaced with fresh solution B. The supernatant was gently stirred and a small aliquot was placed on a haemocytometer and observed with a phase microscope. It was found that the greatest number of cells were separated after 2.5–3 h of digestion.

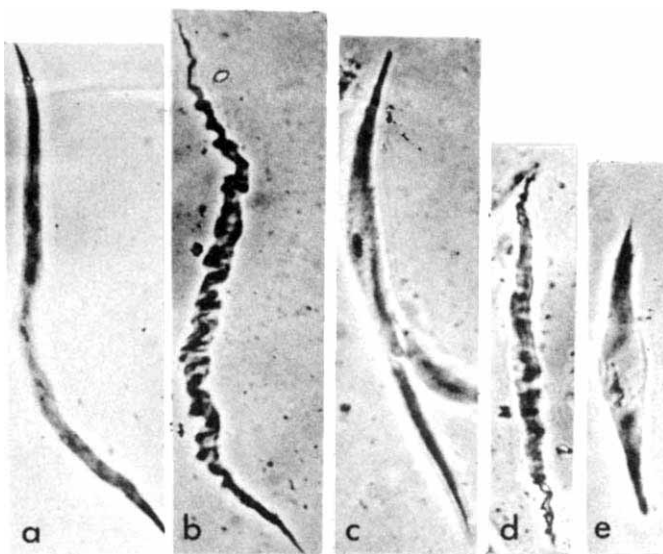


Fig. 1 Examples of cell configurations observed in suspensions of single cells. Phase contrast micrography ($\times 312$).

Various configurations were seen among the cells (Fig. 1). Some were long and spindle-shaped (Fig. 1a), some were slightly contracted to extremely contracted (Fig. 1c, e) while others seemed to be coiled or twisted (Fig. 1b, d). To test for damage to the cells 1% trypan blue in Harris Ringer was mixed with the suspended cells. Lack of staining in 95% of the cells indicated that virtually all cells, regardless of appearance, survived separation⁷. No spontaneous contraction was observed. We tested for contractility by electrical and ionic stimulation.

For electrical stimulation we made a chamber which would produce a sufficient field and which was optically perfect enough for microscopy by cementing cover glasses to a glass slide with epoxy glue so that a shallow trough about 0.15 mm deep and 3–4 mm wide was formed. Two 0.005 inch diameter platinum wires with their ends separated by 3–8 mm were cemented in place with epoxy cement which also served to form the ends of the trough. Silver wires were soldered to the ends of the platinum wires and led to two brass screws fixed to the end of the slide with epoxy glue. Washers and nuts fitted to the screws provided secure, but easily removable, connexion to a Grass SIU5 stimulus isolation unit and S-44 stimulator. The stimulating chamber was mounted on the stage of a Nikon SuKe microscope equipped for photomicrography.

Small samples of supernatant, diluted several times with Harris Ringer to avoid excessive turbidity, were pipetted into the trough, and a cover glass was placed on top. After waiting about 5 min to allow most cells to settle to the bottom, a photomicrograph was taken (Fig. 2a). A single stimulus was delivered to the chamber, and after contraction was maximal a second photograph of the same field was taken (Fig. 2b). Polarizing filters with fibre axes parallel gave the clearest

pictures of cell outlines. The efficiency in achieving contraction in cells depended on duration of stimulus, strength of stimulus and separation of electrodes. With 3 mm separation, a single square-wave pulse of 50 V, 5 ms duration produced maximal contractions in most cells. Not all cells responded to single stimulus, but if a train of 1 ms pulses at 10 Hz was given for 1 to 2 s, virtually all cells contracted. After contraction, cells relaxed slowly, although the cells only occasionally returned to the full length before stimulation. After relaxation, the same cell could be restimulated to contract. We have been able to stimulate a cell to undergo as many as six cycles of contraction and relaxation.

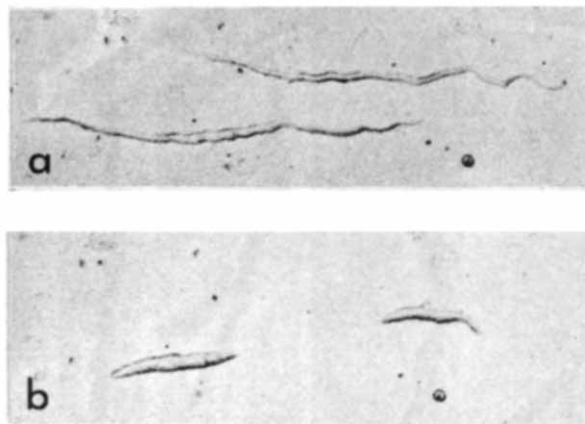


Fig. 2 Micrographs of single cells before (a) and after (b) a single, square-wave pulse. Note the disappearance of convolutions in contracted cells. Photographed with polarization filters, fibre axes parallel ($\times 195$).

We wondered whether the electrical stimulation was activating the cells through the membrane or whether in cells with damaged membranes the electrical stimulus activated the cells by some non-physiological mechanism. To test for a membrane-mediated response, an equal volume of K Harris Ringer (NaCl and NaHCO_3 replaced by equimolar quantities of KCl and KHCO_3) was added to the cell suspension in the trough using a 26-gauge needle and syringe while the cells were observed with a Zeiss inverted-body microscope. Although the currents produced by addition of fluid to the trough made it nearly impossible to observe the same cell throughout, once the addition of fluid had stopped the slide could be moved to an area which showed cells still contracting. As with the repetitive stimulation, nearly every cell contracted in response to the K Ringer. We conclude that the cell membrane is intact and capable of the normal response to a depolarizing stimulus. In every aspect we have been able to test, the isolated cells behave as they do in intact tissue.

We feel that the single cell smooth muscle preparation has great potentialities. For the first time the cellular events in contraction can be observed not just before and after contraction, as was possible with fixed and sectioned material, but throughout a cycle of contraction and relaxation. Furthermore, use of whole cells instead of sections allows three dimensional observation of substructure which permits greater discrimination of changes in organization during contraction. There have been indications that there may be some organization of contractile components into fibrils or other definite patterns (Fig. 1). We are continuing to use single smooth muscle cells in dynamic studies of contraction recorded with microcinematography with the belief that such studies will greatly enhance the understanding of activation and contraction in vertebrate smooth muscles.

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Release of Oxytocin and Vasopressin by the Human Foetus during Labour

OXYTOCIN, a potent stimulant of myometrial activity, is used extensively in clinical practice for the induction of labour. The fact that in animals circulating concentrations of this peptide are increased during labour and maximal at the time of delivery^{1,2} suggests that oxytocin released by the maternal posterior pituitary may play an important part in spontaneous labour. The role of endogenous oxytocin, however, has been disputed. Bioassays suggest that the circulating concentrations are increased to 100 $\mu\text{U/ml}$. or more^{3,4}, while indirect evidence suggests that there is no more than 10 $\mu\text{U/ml}$., and perhaps much less⁵.

It is possible that the high estimates from bioassays in the human are due to non-specific factors, and preliminary data using a specific radioimmunoassay have shown that oxytocin in the maternal circulation does not usually exceed 1 $\mu\text{U/ml}$. (ref. 6). By contrast, oxytocin levels in foetal cord blood taken at the time of delivery are frequently raised⁷, as are those of arginine-vasopressin (AVP)⁸. We have extended these findings, and now present evidence that oxytocin is released by the human foetus throughout labour.

Maternal and foetal blood samples were collected in cooled heparinized syringes and immediately separated at 4°C ; the plasma was acidified to pH 1–2 before storage at -20°C (in which conditions there is no significant destruction of oxytocin by oxytocinase). Oxytocin and vasopressin were extracted and concentrated from plasma, and concentrations estimated by radioimmunoassay as described previously^{7,9–11}. The assays have a maximum sensitivity of 0.75 $\mu\text{U/ml}$. for oxytocin and 4 $\mu\text{U/ml}$. for AVP. None of the materials known to mimic the effects of oxytocin in a biological assay has any effect. AVP shows less than 0.1% of the activity of oxytocin in the oxytocin assay, and oxytocin less than 0.025% of the activity of AVP in the vasopressin assay. The assays can detect exogenous hormone during infusion in normal subjects^{7,11}. The oxytocin assay can detect infused oxytocin in pregnant women, and endogenous hormone in the plasma of goats at the time of delivery⁷.

Oxytocin was undetectable in 81% of samples collected from a forearm vein of women in labour, indicating that concentrations were less than 0.75 $\mu\text{U/ml}$. (Table 1). In the 19% of subjects showing positive results the values ranged from 2–18 $\mu\text{U/ml}$. The sporadic appearance of oxytocin was not related to individual uterine contractions, and serial sampling showed that the presence of detectable concentrations was only transient.

Table 1 Plasma Levels of Oxytocin in Venous Samples obtained from Women during Labour

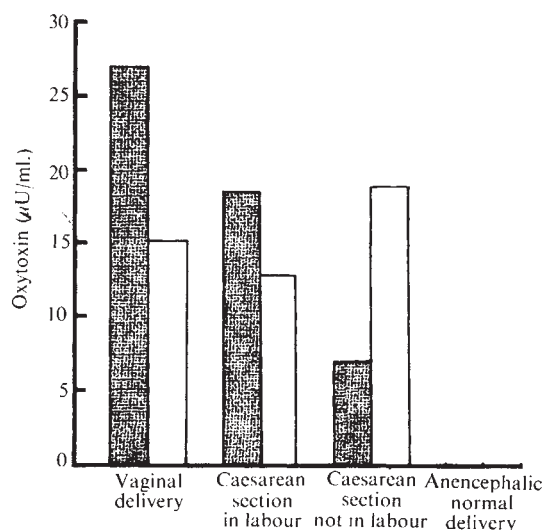
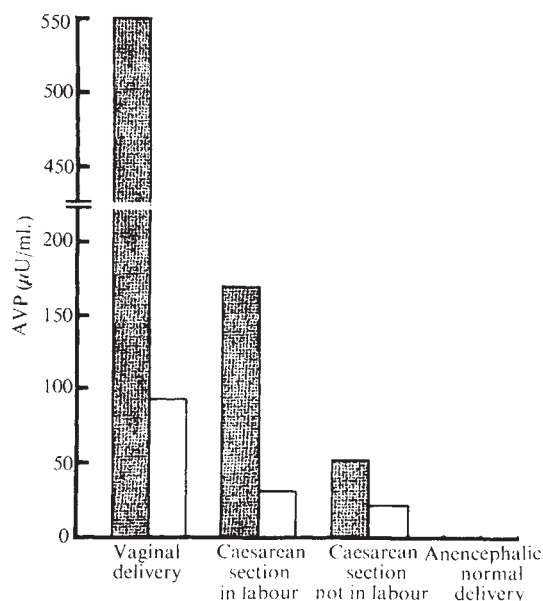
Stage of labour	No. of subjects	No. of samples	Samples containing detectable oxytocin ($> 1 \mu\text{U/ml.}$)		Oxytocin concentrations $\mu\text{U/ml.}$
			No.	% of total	
1st	31	107	24	22	2-12 (mean 7)
2nd	74	74	9	13	2-18 (mean 9)

Oxytocin was detected in 76% of thirty-eight samples of umbilical arterial plasma collected at the time of delivery (Fig. 1). The mean level was $27 \mu\text{U/ml.}$ In paired umbilical venous samples oxytocin concentrations were lower, averaging $15 \mu\text{U/ml.}$ The arteriovenous difference was significant by Student's *t* test ($P < 0.05$). Eight-four per cent of samples showed a positive arteriovenous difference. No oxytocin was detected in either the arterial or venous cord blood of an anencephalic.

In twelve out of sixteen cases of Caesarean section, maternal plasma contained oxytocin, the mean level being $12 \mu\text{U/ml.}$ When the patient was not in labour at the time of operation oxytocin averaged $7 \mu\text{U/ml.}$ in nine samples of umbilical arterial plasma, and $19 \mu\text{U/ml.}$ in paired samples of umbilical venous plasma (Fig. 1). When the patient was in labour the mean umbilical arterial level in four cases was $18 \mu\text{U/ml.}$ and umbilical venous levels $13 \mu\text{U/ml.}$ None of these differences was statistically significant.

Vasopressin was present in 90% of twelve samples of umbilical plasma collected at the time of delivery, the levels averaging $550 \mu\text{U/ml.}$ for arterial samples and $80 \mu\text{U/ml.}$ for paired venous samples (Fig. 2). This difference was statistically significant ($P < 0.001$). None could be detected in the cord plasma of an anencephalic. At the time of Caesarean section umbilical arterial levels of vasopressin averaged $52 \mu\text{U/ml.}$ (arterial) and $21 \mu\text{U/ml.}$ (paired venous) in four cases when the patient was not in labour and $170 \mu\text{U/ml.}$ (arterial) and $32 \mu\text{U/ml.}$ (paired venous) in two cases in labour.

These results suggest that oxytocin release is only a sporadic occurrence in labour, and support earlier evidence that spontaneous uterine activity does not depend primarily on increased concentrations of oxytocin^{1,6}. Three factors could negate this interpretation: (1) the free peptide might be inaccessible to the assay, if oxytocin circulates in bound or precursor form with release at the target organ; (2) the effects of transient release would be smoothed out if oxytocin is bound by the myometrium where it exerts a continuing action;

**Fig. 1** Oxytocin levels in paired samples of foetal umbilical plasma collected at the time of delivery. The stippled areas indicate arterial levels, and the clear areas venous levels.**Fig. 2** Arginine-vasopressin levels in paired samples of foetal umbilical plasma collected at the time of delivery. The stippled areas indicate arterial levels, and the clear areas venous levels.

(3) the levels of oxytocin required to stimulate labour may not be detected by the assay.

Larger concentrations of oxytocin and vasopressin were found in foetal umbilical plasma, suggesting that they originate from the foetal posterior pituitary. This was confirmed by the arteriovenous difference found in most cases, and by the absence of both oxytocin and vasopressin in the cord plasma of an anencephalic, in which there was no morphological evidence of neurohypophyseal tissue. The levels in samples collected at the time of Caesarean section suggest that the release of the hormones occurs particularly during labour. Thus, the arterial levels of oxytocin and vasopressin were greater when the operation was performed during labour than when performed as an elective procedure before the onset of labour.

The stimulus to the release of oxytocin and vasopressin from the human foetal pituitary is not known. A common denominator might be the stress and anoxia associated with delivery, or with the reduction in placental blood flow during contractions, or with the decrease in the functional reserve of the placenta which occurs during the last trimester. The significance of these peptides in the umbilical circulation is also unknown, though it is possible that they exert potent effects on the myometrium and the placental vessels¹². It should be noted that the levels of vasopressin are among the highest recorded in any area of human physiology.

Previous workers have suggested that the foetal anterior pituitary may play a role in delivery¹³⁻¹⁵. Our results indicate that the foetal posterior pituitary may also be involved.

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Cytochalasin B Reversibly Inhibits Melanin Granule Movement in Melanocytes

AGENTS which cause metaphase arrest have been found to affect the rapid reversible darkening of frog skin under the influence of melanocyte-stimulating hormone (MSH)^{1,2}. Darkening is caused largely by the dispersion of melanin granules in dermal melanocytes. After subsequent washing, the skin lightens and the melanin granules aggregate. In this system, preincubation with colchicine, colcemid, vinblastine or vincristine produces a slight increase in darkening induced by MSH, and a dosage-dependent inhibition of the subsequent lightening.

All these agents can bind the cytoplasmic protein that seems to form microtubules³⁻⁸. In melanophores of the teleost *Fundulus heteroclitus*, microtubules are aligned parallel to the direction of pigment movement, and persist whether the melanin granules are dispersed or aggregated^{9,10}. Besides defining the channels in which the pigment moves, it is thought that microtubules may provide the motive force for pigment migration^{9,10}.

In considering the possible role of microtubules in such a motive force, the metaphase-arresting agents, applied to frog skin, are especially useful because their effects are unidirectional; they interfere with lightening of frog skin but not with darkening^{1,2} (colchicine produces a similar effect in *Fundulus melanophores*¹¹). These findings suggest that if a single network of microtubules is responsible for the movement of melanin granules in melanocytes and is disrupted by these agents, it would have to be involved in aggregation and not dispersion. An alternative suggestion⁹ is that in *Fundulus melanophores* there are two interdigitating sets of microtubules with separate activation for aggregation and dispersion. In that case, however, one would have to assume that the microtubules involved in lightening are sensitive to metaphase-arresting agents while those involved in darkening are insensitive. Another alternative is that some other constituents of melanocytes are important for aspects of the movement of melanin granules in relation to microtubules, and suffice for dispersion but not for aggregation. Likely candidates for such a function are the contractile microfilament systems that are involved in motility of cells and within cells, and that are disrupted reversibly by the agent cytochalasin B¹²⁻¹⁴. The effect of this agent on the movement of melanin granules within melanocytes was therefore studied.

Frog skin was mounted on rings and soaked in Ringer

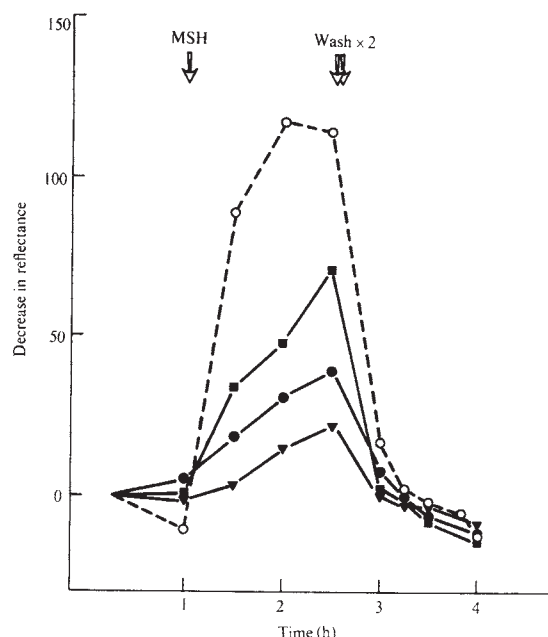


Fig. 1 The effect of cytochalasin B on darkening of frog skin, indicated by a decrease in reflectance. Each treatment group contained one skin specimen from each of four frogs¹⁶. Each point represents the total change in reflectance of the four specimens in that group. Specimens were incubated for 30 min in Ringer solution with or without cytochalasin B, then with MSH (0.5 U/ml.), and were then washed twice in fresh Ringer solution. ■, Cytochalasin B (1 µg/ml.); ●, cytochalasin B (5 µg/ml.); ▼, cytochalasin B (10 µg/ml.); ○, control.

solution to produce an aggregation of melanin granules which, if undisturbed, persisted for several hours. Changes in the state of dispersion of melanin granules were measured as changes in reflectance when the whole skin specimen, immersed in a beaker containing Ringer solution, was placed over a search unit attached to a photoelectric meter^{11,15}. The reading of a given skin specimen after initial soaking was taken as the base line from which subsequent increases or decreases in reflectance were measured.

When cytochalasin B (Imperial Chemical Industries Ltd) was added to this system 30 min before MSH (given by Dr A. B. Lerner, and prepared from a water extract of beef posterior pituitary powder (Armour) as described before¹⁵) there was a dose-dependent inhibition of subsequent darkening (Fig. 1). If the skins were then washed (by changing the Ringer solution), they lightened to a reflectance value near the base line. Controls and skins treated with only 1 µg/ml. of cytochalasin B consistently lightened at least to the base line; skins treated with higher concentrations seldom lightened completely within 2 or 3 h. If MSH was then added again (not shown in Fig. 1), all specimens tended to darken like controls. (Dimethyl sulphoxide (DMSO), in which cytochalasin B was dissolved (at 3 mg/ml.) before being diluted in aqueous media, has no effect on reflectance at similar dilutions.) Thus cytochalasin B seems to inhibit reversibly the dispersion of melanin granules that is induced within melanocytes by MSH.

When the skins were first darkened with MSH and their media then replaced by Ringer solution with or without cytochalasin B, there was some degree of inhibition of subsequent lightening (Fig. 2). If the same skins were then washed, those treated with low concentrations of cytochalasin B (0.5 µg/ml.) tended to lighten like controls; those treated with higher concentrations (for example, 5 µg/ml. in Fig. 2) tended not to return to base line during the period of observation. On subsequent stimulation by MSH, however, all specimens darkened like controls. Thus, in addition to its effect on darkening, cytochalasin B seems to have a less pronounced

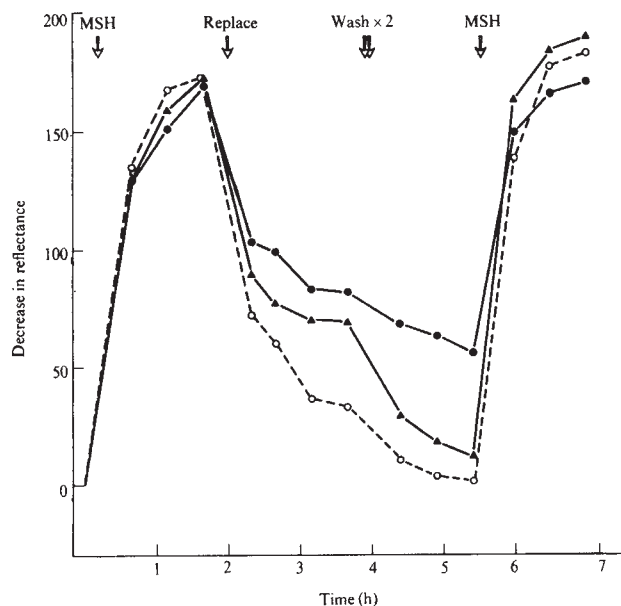


Fig. 2 The effect is seen of cytochalasin B on lightening of frog skin previously darkened by MSH. Specimens were incubated in Ringer solution with MSH (1.5 U/ml.), which was then replaced by Ringer solution with or without cytochalasin B. Later the specimens were washed twice, and still later they were again incubated with MSH. ●, Cytochalasin B (5 µg/ml.); ▲, cytochalasin B (0.5 µg/ml.); ○, control.

effect on the aggregation of melanin granules previously dispersed by MSH.

The interference of cytochalasin B in darkening and lightening of frog skin suggests that a contractile microfilament system is involved in the movement of melanin granules in melanocytes. In frog epidermal melanocytes—which are much smaller than dermal melanocytes and do not contribute significantly to changes in reflectance—melanin granules dispersed by MSH and then treated with cytochalasin B (20 µg/ml.) tend to aggregate, with marked reduction in the number of microfilaments seen (J. McGuire and G. Moellmann, personal communication). In specimens treated with high concentrations of cytochalasin B, the frequent failure of reflectance to return to base line is a secondary effect; such specimens, subsequently treated with MSH, darken like controls (Fig. 2).

A contractile system of microfilaments might provide the motive force for the movement of granules, particularly for their dispersion, while the integrity of microtubules seems also to be important for efficient aggregation. An investigation of the ultrastructure would be useful for further examination of these possibilities.

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Muscarinic Action of Acetylcholine

THE muscarinic excitatory action of acetylcholine on central and peripheral neurones has been suggested to involve a reduction in membrane conductance for potassium ions^{1,2}. This proposal was supported by observations that 2,4-dinitrophenol (DNP) could specifically suppress the excitation by acetylcholine of cerebral cortical neurones in the cat without affecting the excitatory action of L-glutamate, and that the hyperpolarization of these neurones by DNP involved an increase in the membrane conductance for potassium ions³.

We report that the excitation of spinal Renshaw cells by a cholinomimetic which interacts with muscarinic receptors cannot be selectively reduced by DNP. The excitation of these cells by acetyl-β-methylcholine is very sensitive to atropine and is relatively insensitive to dihydro-β-erythroidine⁴, and hence may be assumed to result from an interaction with muscarinic receptors. Experiments were performed on Renshaw cells of the seventh lumbar segments of cats anaesthetized with chloralose (60 mg/kg, intraperitoneal). Extracellular action potentials were recorded with the NaCl-containing central barrel of seven barrel micropipettes, and acetylcholine (bromide, 0.5 M), acetyl-β-methylcholine (bromide, 0.5 M), L-glutamate (Na salt, pH 7.5), DL-homocysteate (Na salt, 0.2 M, pH 7.5) and DNP (Na salt, 0.1 M, pH 9) were administered with suitably directed electrophoretic currents from aqueous solutions in the other barrels.

It was an invariable finding (seven Renshaw cells, five cats) that concentrations of DNP (anionic currents of 40–60 nA) which reduced the sensitivity of Renshaw cells to acetyl-β-methylcholine had a quantitatively similar effect on the sensitivity to acetylcholine, L-glutamate and DL-homocysteate. Concentrations adequate to completely block the action of the cholinomimetics also abolished that of the excitant amino-acids and spontaneous firing: such effects were often associated with a reduction in the amplitude of extracellularly recorded action potentials and were fully reversible. Although these results would be consistent with a hyperpolarizing action of DNP³, which might reasonably be considered to diminish the apparent effectiveness of all excitants, the effect of DNP on Renshaw cells may be more closely related to processes involved in the generation of action potentials and hence also relatively non-selective towards excitants. Preliminary experiments indicate a similar, but not readily reversible, effect of iodoacetate.

Thus the effects of DNP on acetylcholine sensitive cortical neurones may not be directly applicable to the mechanisms of activation of muscarinic receptors on neurones elsewhere in the nervous system.

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Regulation of Adenosine 3',5'-Cyclic Monophosphate Metabolism in Cultured Neuroblastoma Cells

MOUSE neuroblastoma C-1300 has a large number of electrical, biochemical and morphological properties characteristic of differentiated neurones¹⁻⁹. The cell line is thus particularly useful as a model in which neuronal functions can be studied in a clonal propagating system *in vitro*.

The study of neurohormonal receptors in such cells is interesting, and both depolarizing and hyperpolarizing responses to acetylcholine have been noted^{7,10}. We have investigated whether receptors in these cells were demonstrable by virtue of their ability to stimulate the accumulation of intracellular adenosine 3',5'-cyclic monophosphate (cyclic AMP).

Clonal lines of neuroblastoma C-1300 derived by Dr T. Amano were grown routinely in Falcon plastic bottles in Dulbecco's modified Eagle medium, supplemented with 10% foetal calf serum, penicillin G (50 U/ml.) and streptomycin sulphate (10 µg/ml.), in an atmosphere of 10% CO₂ and 90% air. Cells were subcultured by brief incubation in a divalent cation-free medium (saline D₁¹¹ with 5.6 mM glucose and 59 mM sucrose to maintain isotonicity with growth medium). Cell lines were free of contamination by PPLO as determined by culture and by autoradiography following incubation with ³H-thymidine (R. Dulbecco, personal communication).

For experimental study, cells were plated on 25 mm diameter glass cover slips and grown as described previously¹² for 5–6 days. Experimental incubations were performed in 2 ml. of medium minus serum at 37° C with an atmosphere of 90% air and 10% CO₂. Theophylline (1 mM) was present, except where indicated, during a preliminary 60 min incubation. Compounds to be tested were then added for 15 min of additional incubation, except where indicated. Finally, the medium was aspirated, the cells were fixed and the cyclic AMP extracted with 5% trichloroacetic acid (TCA). This technique is quantitative and seems to be virtually instantaneous. Cyclic AMP was analysed and assay specificity was verified as previously described¹³. Cellular material was quantified by determination of precipitated protein after solubilization in 0.2 N NaOH, by a modification of the method of Lowry¹⁴. An average cell sample contained 500 µg protein.

Table 1 Effect of Chemical Agents on Cyclic AMP Levels of Neuroblastoma Clones

Treatment	Neuroblastoma clone			
	N4TG1	S20	N18	N10
	Cyclic AMP (pmol/mg protein)			
H ₂ O control	14	15	15	30
Isoproterenol, 10 ⁻⁴ M	13	14	20	28
Histamine, 10 ⁻⁴ M	14	13	21	30
5-Hydroxytryptamine, 10 ⁻⁴ M	14	15	18	31
PGE ₁ , 2.9 × 10 ⁻⁶ M	141	44	42	129
PGF _{2α} , 2.9 × 10 ⁻⁶ M	19	16	18	36
Minus theophylline	26	13	13	36
Minus theophylline + adenosine, 10 ⁻⁴ M	28	13	13	38
H ₂ O control				36
Dopamine, 10 ⁻⁴ M				39
Carbamylcholine, 10 ⁻⁴ M				39

Four clonal lines of neuroblastoma have been found to have control levels of cyclic AMP ranging from 15–35 pmol/mg protein and have been tested with catecholamines, histamine, 5-hydroxytryptamine, adenosine, and prostaglandins E₁ and F_{2α} (PGE₁ and PGF_{2α}) (Table 1). Only PGE₁ was found to be an effective stimulant, but it was active in all lines examined. One line (N10) was accordingly selected for further study, and in these cells responses to PGE₁ were independent of the cellular growth phase. This clone failed, in addition, to respond to carbamylcholine or dopamine.

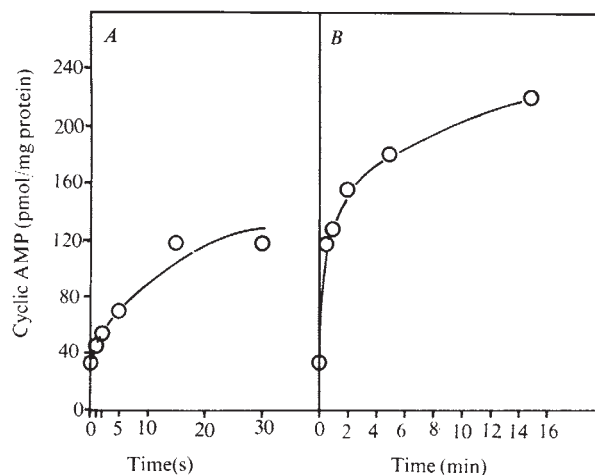


Fig. 1 Time course of response to PGE₁. For short incubation times (A), cover slips with adherent cells were dipped in beakers of PGE₁ (2.9 × 10⁻⁶ M) and then fixed in 5% TCA. For longer incubations (B), PGE₁ (2.9 × 10⁻⁶ M) was added to beakers containing cover slips and medium.

The time course of the effect of PGE₁ to stimulate cyclic AMP accumulation in these cells is shown in Fig. 1. The cover slip technique allows rapid manipulation of cell monolayers, minimizes diffusion time, and thus permits examination of short incubation times. Elevated intracellular levels of cyclic AMP were apparent after 1, 2 and 5 s of exposure to PGE₁. The rapidity of change of the total intracellular cyclic AMP content suggests that local changes of cyclic AMP concentration can occur with sufficient speed to mediate rather short latency effects of neurotransmitters. Maximal levels of cyclic AMP were attained by 5–15 min. While levels declined somewhat after 15 min (data not shown), cells maintained intracellular levels of cyclic AMP in excess of 100 pmol/mg protein 24 h after the addition of 2.9 × 10⁻⁵ M PGE₁ to growth medium minus serum.

The effects of PGE₁ concentration and of theophylline are seen in Fig. 2. Other data (not shown) indicate that responses seen at 2.9 × 10⁻⁶ M PGE₁ were nearly maximal. The PGE₁ concentration for a half-maximal effect is thus approximately

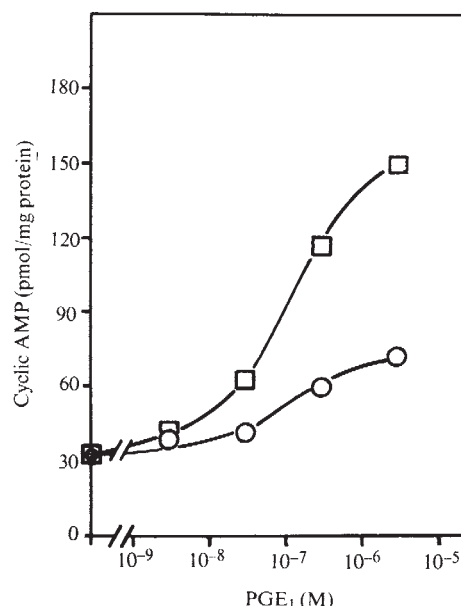


Fig. 2 Effect of PGE₁ concentration and theophylline. Cells were incubated for 60 min in the presence (□) or absence (○) of 1 mM theophylline. The indicated concentrations of PGE₁ were then added for 15 min of additional incubation.

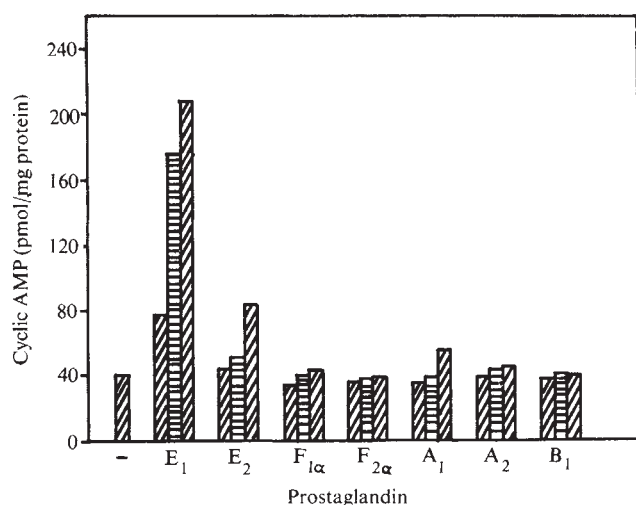


Fig. 3 Relative potencies of prostaglandins. Control level of cyclic AMP is shown by single bar to left. The indicated prostaglandins were tested at 2.9×10^{-8} M, 2.9×10^{-7} M, and 2.9×10^{-6} M (bars from left to right, respectively).

10^{-7} M. Theophylline (an inhibitor of cyclic nucleotide phosphodiesterase) potentiated the effect of PGE_1 two to threefold, indicating that PGE_1 stimulates cyclic AMP synthesis.

The relative potencies of various prostaglandins are seen in Fig. 3. Prostaglandin E_1 was the most effective. PGE_2 showed definite activity at 2.9×10^{-6} M, and an effect of PGA_1 at 2.9×10^{-6} M was probable. Higher concentrations of these materials have not been tested.

The significance of the above data is two-fold. Prostaglandins have been shown to be released with neural activity and to have significant behavioural and other central nervous effects^{15,16}. Their possible role as neurotransmitters has been discussed^{15,17}. Prostaglandins of the E series have, moreover, been shown to antagonize the effect of norepinephrine to

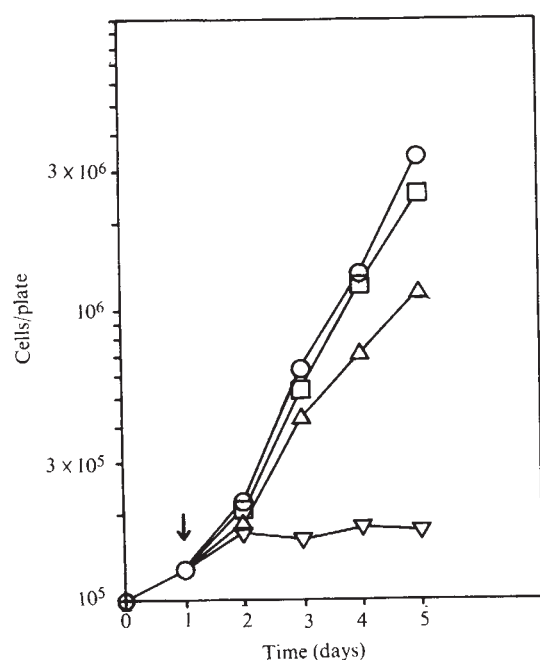


Fig. 4 Effect of PGE_1 and theophylline on cell division. Cells were plated at a concentration of 1×10^5 cells/60 mm dish. On day 1 compounds were added to growth medium as follows: growth medium alone ($\circ$); 1 mM theophylline ($\square$); 1.5×10^{-5} M PGE_1 ($\triangle$); 1 mM theophylline plus 1.5×10^{-5} M PGE_1 (∇). Medium was changed and drugs were added daily. Cell counts were performed on duplicate plates with a haemocytometer.

hyperpolarize and inhibit the rate of discharge of Purkinje neurones¹⁸. While direct evidence is unavailable, this effect of PGE_1 is presumably due to its ability to inhibit noradrenaline stimulation of the accumulation of cyclic AMP in this cell. Both inhibitory and stimulatory effects of prostaglandins on intracellular levels of cyclic AMP are, however, well known¹⁹.

The stimulatory effect of PGE_1 on cyclic AMP levels allows one to produce both rapid and long lasting changes in the intracellular levels of the nucleotide in this model system. This ability should greatly facilitate the investigation of possible effects of the cyclic nucleotide on the differentiated neuronal properties exhibited by these cells. Many of the differentiated functions of these neuroblastoma cells, however, are expressed with far greater intensity when cell division is slowed at cellular confluency or by other means^{4,5,9}. Before effects of PGE_1 or cyclic AMP on these parameters can be studied, it is necessary to evaluate their effects on cell growth. High concentrations of exogenous cyclic AMP have been shown to slow the rate of division of HeLa and other cells^{20,21}. Pastan *et al.* have recently reported that dibutyryl cyclic AMP or PGE_1 inhibits growth of certain lines of fibroblasts²².

Effects of PGE_1 and theophylline on the rate of cell division of neuroblastoma cells are shown in Fig. 4. After an initial lag, control cells grew logarithmically and doubled in less than 24 h. While theophylline alone had no effect on cell multiplication, PGE_1 inhibited markedly—only one-third as many cells were present on day 5 in 1.5×10^{-5} M PGE_1 as in control plates. The combination of PGE_1 and theophylline virtually prevented accumulation of cells. The two agents thus potentiated each other here, as also shown when cyclic AMP levels were examined (Fig. 2).

Our data show a stimulatory effect of PGE_1 on cyclic AMP accumulation in a neuronal tumour cell and represent, we believe, the first demonstration of an effect of any potential neurohormone on the cyclic AMP level of a defined cell of neural origin. In addition, effects on cell division such as those described suggest that factors regulating cyclic AMP levels may affect the course of cell differentiation or provide mechanisms for cell selection during development.

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Čerenkov Light from ^{32}P as an Aid to Diagnosis of Eye Tumours

THE ^{32}P uptake ratio test¹ as an aid to tumour diagnosis has had limited success for tumours in the posterior half of the eye²⁻⁴. Phosphorus is incorporated preferentially in dividing rather than non-dividing cells⁵ and so, in essence, all the test requires is the oral or intravenous administration of ^{32}P orthophosphate (typically 100–500 μCi) and the β radiation from the lesion is measured and compared with that over the surrounding normal tissue.

In practice the test is complicated mainly by two factors. Inflammatory and certain other actively metabolic lesions will also incorporate ^{32}P in preference to normal quiescent tissue; and because β radiation has a short mean path length (3 mm in tissue), the placement of the detector is critical.

The problem of inflammatory lesions is largely overcome by spacing two observations of uptake to 4 and 24 h after administration of the isotope^{4,6}. The inflammatory and metabolic components of uptake at 4 h greatly decrease by 24 h because of the rapid turnover of phosphorus in these processes. Thus one criterion reported for a positive diagnosis of malignancy⁶ is that the uptake at both 4 and 24 h with respect to surrounding normal tissue has to be greater than a ratio of 1.5:1.

The placement problem is particularly acute when the test is applied to lesions posterior to the equator of the eye, for which surgery of access is most often necessary. Most eye tumours arise in this region in the choroid.

However, it is possible to detect the presence of ^{32}P in the back of the eye by observing the Čerenkov light produced by the passage of the β radiation in the vitreous humour. This can be done quite simply through the pupil using a highly sensitive photomultiplier tube.

From the theory of the Čerenkov effect it may be shown that the average radiation from ^{32}P in water will produce about thirty visible photons⁷ per emitted β particle, and this has been used with transparent solutions of ^{32}P -labelled compounds in liquid scintillation counters⁸.

I have investigated the use of this effect as a simple diagnostic test for the presence of ^{32}P in the posterior half of the eye. A specially selected bi-alkali type of photomultiplier tube was obtained (Centronic type 4249). This has a background emission of only 3 electrons/s from the cathode. It was coupled to a short length of 'Perspex' light pipe which was positioned over the eye of an anaesthetized rabbit, in contact with the cornea. When 0.8 mCi of ^{32}P was injected intravenously into the medial ear vein a signal of 400 pulses/s was produced from the photomultiplier tube. After a few minutes observation, a 0.0005 inch layer of black tape was placed over the end of the light pipe. The count rate fell to

80 pulses/s, which represented the fraction of Čerenkov light created in the light pipe by primary β irradiation. Thus the bulk of the signal detected by the photomultiplier tube can be attributed to Čerenkov light emanating from the vitreous humour as a result of the circulation of ^{32}P through the highly vascular choroid.

This test for Čerenkov emission should, therefore, provide a sensitive means of readily detecting and quantitating ^{32}P incorporated by ocular lesions and its applicability to the diagnosis of human ocular melanomata is planned.

Facilities and assistance for this work were provided by Dr H. A. S. van den Brenk of the Richard Dimbleby Cancer Research Laboratory, St Thomas' Hospital, and I am indebted to the research committee of the hospital for a grant to purchase the apparatus. The detector housing assembly was built by Mr A. Lee.

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Transfer of Blastocysts as Applied in Experimental Teratology

It is well known that genetic constitution modifies the effect of teratogenic agents (Table 1). The most obvious example is the varying susceptibility of different strains of mice to teratogens such as cortisone, 6-amino-nicotinamide and salicylates¹⁻⁵. In A/Jax mice, for example cortisone induces cleft palate in 100% of living embryos (if those with spontaneous cleft lip-palate—about 10% of births—are excluded). Isolated cleft palate can be induced with cortisone in only about 20% of embryos in other strains such as C57Bl and CBA^{1,3}.

Reciprocal cross differences demonstrated in the frequency of cleft palate induced by cortisone³ or foetal death induced by salicylate⁵ are matroclinal; the maternal influence could be chromosomal, cytoplasmic or uterine (Table 1). The maternal chromosomal effect would be transmitted with the *X* chromosome and the effect would thus be seen in the males, but cleft palate induced by cortisone is distributed equally among male and female embryos³. A cytoplasmic factor seems to be responsible for the differing susceptibility to 6-amino-nicotinamide in A/Jax and C57Bl mice⁶, but Kalter could not demon-

Table 1 Genetic Factors modifying the Effect of Teratogenic Agents

Factors	Revealed by
1 Strain difference	Reciprocal crosses $A \times B$ $B \times A$
2 Paternal influence	
3 Maternal influence	
(a) chromosomal	Increased risk in males Back crosses $(A \times B) \times A$ $(B \times A) \times A$
(b) cytoplasmic	
(c) uterine	
	Egg transfer

strate such a cause of the susceptibility of A/Jax mice to cleft palate induced by cortisone³. The uterine environment is known to affect foetal growth⁷. By the technique of egg-transfer McLaren and Michie⁸ demonstrated that the maternal effect on the number of lumbar vertebrae in mice was caused through the uterus. We have now investigated the possibility of transferring blastocysts in experimental teratology. The technique provides controlled experimental conditions, which cannot be obtained with time consuming back crosses.

Although the most common transfer method is to inject blastocysts into a free-dissected uterine horn (see review by Rafferty⁹), we chose a non-surgical technique¹⁰, which we have modified. Three day old blastocysts (vaginal plug=day 0) were flushed from the uterine horn with Krebs Ringer solution and sucked from a watch-glass into a micro-pipette (Microcap) with an external diameter of 0.6 mm and maximum volume of 0.2 μ l. A piece of a plastic tube was placed in the vagina as a speculum. Recipients were anaesthetized with a small intraperitoneal dose of a 2% solution of tribromo-ethanol (TBE); the blastocysts were expelled by gentle pressure into the horn. In addition to the transfer experiments reciprocal crosses were performed.

We knew that if cortisone is given intramuscularly during days 11, 12, 13 and 14 of gestation cleft palate is induced in 100% of A/Jax mice and in 12–20% of CBA mice¹. Reciprocal crosses showed us (Table 2) that foetuses growing in an A/Jax mother developed a higher percentage of cleft palate than those in a CBA mother. There was no male dominance in the cleft palate groups, excluding the possibility of a pure X-linked inheritance. As the autosomal genome must be identical in the two crosses we have two alternative explanations—cytoplasmic factors, inherited through the egg, or uterine influence.

Table 2 Cortisone-induced Cleft Palate in Mice after Reciprocal Crosses

Mother	Father	(%)	Cleft palate		(♂)	Litters
			(♀)	(No.)		(No.)
A/Jax	× CBA	68	19	45	26	11
CBA	× A/Jax	34	14	34	20	15

Cortisone, 62.5 mg/kg/day, was given intramuscularly on gestation days 11, 12, 13, 14.

Blastocyst transfer was controlled so as not to cause cleft palate in eighteen transferred A/Jax × A/Jax embryos to 11 CBA foster mothers. Homozygous CBA blastocysts were transferred to A/Jax foster mothers and *vice versa* (Table 3). As the recipients were mated with fertile males of their own strain, controls to the transferred foetuses were obtained within the same mother. Difference in eye pigmentation makes it easy to distinguish the two strains. The results, moreover, clearly demonstrate that transferred A/Jax × A/Jax foetuses are not protected in the CBA uterus; they all develop cortisone-induced cleft palate. Only 20% of CBA × CBA foetuses in CBA mothers had cleft palates. Even though only a few living CBA × CBA foetuses were transferred to A/Jax foster mothers, it was clear that there was no increase in frequency of cleft palate over the original 20%. Thus, the maternal influence observed in the reciprocal crosses cannot be interpreted as uterine.

Our modified technique of blastocyst transfer thus seems to be of value not only for studying the morphological malformations in the orthodox sense of teratology but also for problems more related to foetal pharmacology.

Table 3 Cortisone-induced Cleft Palate in Mice after Blastocyst Transfer

Genotype of embryos		Mothers	Cleft palate		Litters
Transplanted	Controls		(%)	(No.)	
A/Jax × A/Jax		CBA	100	32	12
	CBA × CBA	CBA	20	11	12
CBA × CBA		A/Jax	22	4	12
	A/Jax × A/Jax	A/Jax	100	40	12

Cortisone, 62.5 mg/kg/day i.m., on gestation days 11, 12, 13, 14.

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Transformation of Human Leucocytes by Throat Washing from Infectious Mononucleosis Patients

A SIMPLIFIED procedure for studying induced transformation of human leucocytes *in vitro*¹ utilizes umbilical cord blood leucocytes which are easily obtained and do not transform spontaneously. When treated with cell-free filtrates from lymphoblastoid cell lines of a mononucleosis patient and three healthy persons, cord blood leucocytes were transformed to rapidly and persistently multiplying lymphoblasts^{2,3}. Chemical carcinogens and ionizing radiation were ineffective². In a long term search for transforming agents in the human environment, we have studied numerous agents including the secretion from upper respiratory tract of mononucleosis patients. We found that their secretion contained transforming activity.

Infectious mononucleosis was diagnosed on criteria proposed by Hoagland⁴. Secretion from the upper respiratory tract of eight patients was collected by gargling with 10 ml. of tissue culture medium¹, 5 to 17 days after onset of illness. Throat washings were filtered through a 0.45 membrane filter and the filtrate stored at below -60°C until use.

Umbilical cord blood leucocyte suspension, 5×10^6 leucocytes/ml. of nutrient medium, was prepared¹ and 0.5 ml. of filtered throat washing was mixed with 1 ml. of leucocyte suspension. Uninoculated leucocyte cultures from the same specimen of cord blood were similarly treated as control.

Four of the eight throat washings had transforming activity, evidenced by the ability to induce the formation of large aggregates of small round cells and increase in the number of viable cells as early as the third or fourth week after inoculation. Transformed leucocytes resembled lymphoblasts in appearance and multiplied rapidly and persistently. All four transformed cultures have been subcultured twenty-two times at intervals of 3 or 4 days, and are still growing actively. As expected, the eight uninoculated control cultures were not transformed. The experiment was repeated with the four positive throat washings and these also had transforming activity.

The transformed leucocytes were assayed three times for Epstein-Barr virus (EBV) antigen by the indirect immunofluorescent test⁵, but the results were inconclusive as all transformed cultures contained γ globulin-secreting cells.

The importance of our work is that it is the first detection of a leucocyte-transforming agent, which must be considered potentially oncogenic for man, in human upper respiratory tract secretion. Further investigation into the nature of this transforming agent may clarify its relationship with (a) EBV, (b) transforming agents from various lymphoblastoid cell lines (from Burkitt's lymphoma^{6,8}, acute leukaemia⁷, mononucleosis patients², and healthy persons³) and (c) the filtrable agent which can convert lymphoid cells from negative to positive for EBV antigen⁹.

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Salmon Nomenclature

Payne, Child and Forrest¹ have shown little regard for the rules of zoological nomenclature in proposing the subspecific names "europaeus" and "americanus" for the Atlantic salmon, *Salmo salar*. First, the European stock, binominally named by Linnaeus, must become the nominate subspecies and, therefore, should bear the name *Salmo salar salar* Linnaeus, 1758² rather than *S. salar europaeus*. Second, a cursory examination of the literature reveals a number of older and available names for the North American stock. These include *S. immaculatus* Storer 1950³, *S. sebago* Girard 1854⁴, *S. gloveri* Girard 1856⁵ and *S. ouananiche* McCarthy 1894⁶, any of which must take precedence over *S. salar americanus*. Undoubtedly any British ichthyological systematist could advise the authors on correct choice of names for their subspecies. At the same time, they should consider that while designation of type-specimens in the species group is not mandatory, it is a protocol to which systematists almost invariably adhere⁷.

Although the authors are aware of "communal feeding grounds off Greenland" for both European and South American salmon stocks, they seem to be unaware that some salmon spawn in Greenland⁸. The transferrin type of this Greenland stock is apparently unknown, but could be intermediate between the European and American stocks. Furthermore, the small size of their North American sample (only seventy-eight specimens) from a geographically restricted area is hardly comparable with the large sample from the British Isles (4,414 specimens). Perhaps the authors would be advised to test their hypothesis on a larger sample from North America as well as

samples from Greenland and European localities other than the British Isles before they take the step of proposing corrected subspecific names for these salmon stocks.

Finally, however, they are only able to distinguish 57.7% (forty-five out of seventy-eight specimens) of their North American sample from their European sample. Few taxonomists would agree that such a low percentage discrimination deserves subspecific designation.

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Drs Payne, Child and Forrest write: Dr Gruchy's criticism of our proposed nomenclature is quite valid and we accept that the European subspecies of the Atlantic salmon should be called *Salmo salar salar* L. according to the International Code of Zoological Nomenclature. The choice of a correct name for the North American stock is more difficult in view of the complexity of earlier terminology and a detailed study of the literature is indicated.

Our thesis is that free gene exchange was possible through the amphi-Atlantic range of *S. salar* until the end of the Last Inter-Glacial when the expansion of the polar ice-cap caused a major discontinuity in the range. We believe that genetic contact has never been re-established as shown by the restriction of the transferrin variants Tf3, Tf4 to North America and Tf2 to Europe (one must assume that Tf1 was the "ancestral" gene at this locus and that Tf2, Tf3 and Tf4 have arisen by mutation at this locus since the establishment of a geographical barrier in the polar region of the North Atlantic). We do not conceive of these transferrin variants as definitive characters for the recognition of morphological subspecies but as indicators of the existence of a major discontinuity in the free exchange of genetic material through the species. However, we hope that absolute discriminants may be discovered from further work.

An analysis¹ of 1,623 Atlantic salmon sera collected over the area between Labrador and Maine showed that there is a widespread polymorphism in transferrin phenotype which is determined by three allelomorphous genes. It is highly probable that these alleles correspond with Tf1, Tf3 and Tf4 described in our paper. This work confirms that the transferrin polymorphism we describe in the salmon populations of the Gulf of St Lawrence is not a feature applicable only to this geographically restricted area.

We have not examined material from the very small native population in Greenland. However, an analysis of more than 1,000 sera samples from the drift-net fishery in the Davis Strait between West Greenland and Canada did not reveal any intermediate phenotypes (Tf2/Tf3, Tf2/Tf4). We have examined a small sample (100 specimens) from rivers in SW Iceland; all these fish had the Tf1 phenotype. While further work in this area is required, this must be taken as provisional evidence that the Tf3 and Tf4 alleles have not spread from North America into the European side of the North Atlantic via Greenland.

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GENERAL

Balancing Mutual Force Reductions

THE problem of reducing conventional forces in the European setting in a balanced manner as between the forces of the NATO and Warsaw Pact countries is of some political interest. Here I set out to provide logical baselines, using a mathematical approach but without indulging in massive computation, for deciding when, and in what sense, small force reductions involving two opposing parties might be said to be balanced. Three different approaches to the question are made, each based on essentially different but plausible idealizations of what balanced reductions in military strength may mean, or may be taken to mean by the parties concerned.

This first approach begins by assuming that there is, before any reductions, a balance between the two parties, A and B , and that this balance can be represented in general by an equation of the form

$$g(M_A, T_A, P_A, N_A, \dots) = f(M_B, T_B, P_B, N_B, \dots) \quad (1)$$

where g and f are the war-fighting capabilities of A and B respectively, and are functions (unknown) of the respective numbers of troops (M), tanks (T), aircraft (P), tactical nuclear weapons (N) and so on deployed by each side. From equation (1), for small reductions in troops, say, ΔM , it follows that

$$\Delta M_A / \Delta M_B = \partial M_A / \partial M_B \quad \text{and} \quad \frac{\Delta T_A}{\Delta T_B} = \frac{\partial T_A}{\partial T_B} \quad \text{and so on} \quad (2)$$

and we can say that the reductions, $\Delta M_A / \Delta M_B$, are balanced when equation (2) is satisfied.

It is convenient to proceed by making the further assumption that the existing level of forces came about as the result of an arms race, fitting either the well known but crude Richardson model¹, or some modern variant of it such as Caspary's², and which has reached a stage of zero growth rate in the armaments expenditure of both sides.

For zero growth rate in expenditure both the Richardson and the Caspary models reduce to the simple form

$$M_A \div k M_B \quad (3)$$

where k is a dimensionless constant incorporating the Richardson constants¹ and a factor translating financial expenditure into troop levels (the equation is inexact because of the assumption, very nearly correct, that recurring expenditure on each side of the European conventional military confrontation is predominantly, directly or indirectly, on manpower)

Combining equations (2) and (3) now gives

$$\Delta M_A / M_A \div \Delta M_B / M_B \quad (4)$$

and assuming that the ratio of tank numbers to troop numbers within a fighting force should remain approximately fixed, it follows from equation (4) that

$$\Delta T_A / T_A \div \Delta T_B / T_B \quad (5)$$

Thus within the meaning of balance as it has been understood in this section it seems that for small ground force reductions to be carried out in a balanced way they should take the form of equal percentage cuts.

The second approach assumes not only that there is a balance but also that this balance is stable in the sense that an outbreak of hostilities would lead to no advantage, initially at least, for either side. Small peacetime reductions in forces related in the same way as those that might be expected to occur in the earliest stages of an outbreak of hostilities are then said, in the sense of the term as used here, to be balanced.

If, first of all, we treat the initial outbreak of hostilities for the sake of simplicity as a tank battle, the least complicated equations which seem to satisfy the more obvious requirements of a representation of respective tank losses on the outbreak of hostilities are

$$\begin{aligned} dT_A/dt &= -pT_AT_B + R(t) \\ dT_B/dt &= -qT_AT_B + S(t) \end{aligned} \quad (6)$$

where R and S are reinforcement functions of time (t) measured from the outbreak of hostilities and which tend to zero as t tends to zero; and p and q are measures of the "killing" rates of the tanks of B and A respectively.

Putting t equal to zero equations (6) give approximately for the tank losses ΔT_A and ΔT_B

$$\Delta T_A / T_A = p/q \frac{\Delta T_B}{T_B} \left(\frac{T_B}{T_A} \right) \quad (7)$$

At this stage a further assumption needs to be made concerning the scenario for the tank battle: this is that the numerically larger tank force (let us say T_A) is taken to be the attacker. It is then possible to ascribe a value to p/q because it is fairly generally accepted³ that tanks can more effectively destroy other tanks from a defensive position than the other way round. If the current NATO tank strength in the NATO Northern and Central Theatres of Europe is assumed accurately to reflect this superiority of the defence in the sense that $p/q = T_A / T_B$, then equation (7) becomes

$$\Delta T_A / T_A = \Delta T_B / T_B \quad (8)$$

If, however, p/q is taken to be a fixed ratio derivable from the study and observation of historical conflicts and weapons trials, and Ogorkiewicz seems to put its value at around 4 in this context³, then equation (7) becomes

$$\Delta T_A / T_A = 4 \Delta T_B / T_A (T_B / T_A) \quad (9)$$

Inserting the ratio T_B / T_A of the current NATO to Warsaw Pact tank forces in the Northern and Central Theatres of Europe⁴ equation (9) now becomes

$$\Delta T_A / T_A = 1.6 \Delta T_B / T_B \quad (10)$$

Alternatively the outbreak of hostilities can be represented in a more general way if we accept Lanchester's theorem^{2,5} that the "fighting strength" of a force is proportional to the square of the number of units of that force. If we can take it that the condition that the outbreak of hostilities leads to no initial advantage for either side can be met by equating the initial "fighting strengths" of each side, then according to whether we view the outbreak of hostilities as a troop engagement with tanks as firepower or as a tank battle supported by troops, we have

$$M_A^2 = u M_B^2 \quad (11)$$

or

$$T_A^2 = v T_B^2 \quad (12)$$

where u and v are dimensionless constants. From equations (11) and (12) for small losses ΔM in troops and ΔT in tanks we obtain

$$\Delta M / M_A = \Delta M_B / M_B \quad (13)$$

$$\Delta T_A / T_A = \Delta T_B / T_B \quad (14)$$

Thus for small peacetime reductions in tank forces of the NATO and Warsaw Pact alliances in the Northern and Central Theatres of Europe to be balanced in the sense of the term used here they must lie somewhere between the equal percentage reductions suggested by equations (8) and (14), and percentage reductions approximately in the ratio 3 to 2 in favour of the smaller force according to equation (10). Troop reductions, using the arguments of the previous section fortified by equation (13), should be within the same range of proportions.

Finally, the existing disposition of forces may be in balance in the sense that both sides A and B perceive the existence of a situation of mutual deterrence, each side being convinced that a surprise attack by either will leave intact too large a proportion of the original fighting strength of the defender (his second strike force) to make the attack worthwhile. For conventional forces the problem of what then constitutes balanced peacetime reductions is most easily handled in terms of tactical air strength.

Assuming for the moment that both A and B will, plausibly, regard peacetime reductions in numbers of aircraft as balanced

when they leave the existing expected ratio of second strike strengths unaltered, we can find an expression for this ratio if we can write the numbers of second strike aircraft as P_A^0 and P_B^0 where

$$P_A^0 = P_A(1 - c_A)^{f_B P_B P_A / P_A} \quad (15)$$

$$P_B^0 = P_B(1 - c_B)^{f_A P_A P_B / P_B} \quad (16)$$

and P_A, P_B are the existing numbers of aircraft; c_A, c_B the probabilities that on average P_A and P_B aircraft will be destroyed before take off by one aircraft of the forces of B and A respectively; and f_A, f_B are the fractions of the airforces of A and B devoted to a first strike disarming attack.

Then dividing equation (15) by equation (16) and differentiating we obtain after some manipulation

$$dP_A/dP_B = P_A/P_B \quad (17)$$

which becomes, after equating the small peacetime reductions in aircraft numbers ΔP_A and ΔP_B to the differentials,

$$\Delta P_A/P_A = \Delta P_B/P_B \quad (18)$$

from which and from equations (15) and (16) it also follows that

$$\Delta P_A^0/P_A^0 = \frac{\Delta P_B^0}{P_B^0} = \Delta P_A/P_A \quad (19)$$

Thus not only are reductions in numbers of aircraft balanced in the sense of this section when they are carried out in equal percentages according to equation (18) but also, provided they are accompanied by numerically equal percentage reductions by both sides in troops and tanks, the new, smaller second strike tactical aircraft forces will automatically be in the same ratio to the new number of military targets (troops, tanks and aircraft) possessed by the other side as are the existing second strike forces to the existing number of military targets. (This will not be precisely true since there are second strike targets for tactical aircraft, such as bridges, fortifications and certain townships, the number of which will scarcely, or only indirectly, be affected by reductions in military equipment and personnel.) This important result clarifies and supports the original assumption that tactical aircraft reductions which preserve in being the existing ratio of second strike forces could be taken as balanced by the parties involved.

As a prescription for the way in which "balanced" force reductions in Europe should be carried out this paper does not pretend to completeness. In particular it does not deal with the question of how large such reductions should be, only their inter-relationships, although the technique of analysis is usually based on a presumption of small, up to 10%, reductions.

This article sets out to put the case for equal or near equal percentage cuts as being most likely to preserve the existing balance of conventional military strength, over the wide spectrum of meanings given to that phrase. And the plausibility of this proposition gains considerably from the consistency with which it emerges from the three approaches to the problem.

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Supernatural Beliefs of Graduate Students

In their recent report entitled "Supernatural Beliefs Among Graduate Students at the University of Pennsylvania"¹, Salter and Routledge examined the hypothesis that further education leads to a decline in supernatural beliefs, an idea already tested in a population of undergraduate males². Their sample, however, was strongly biased in favour of male students with one year of graduate study and limited to married students living in a university campus residence hall, and therefore was unrepresentative of the total graduate student population. Of the 9,000 graduate students, approximately 50% are married and, of these, only 10% live in university campus housing.

We doubt the precision of the method used to measure the extent of an individual's belief in the supernatural. Each subject was rated on a scale from 0 to 20 according to his assessment of strength of his belief in certain phenomena. It is not clear if he was rated by himself or by the interviewer. Zero indicated total unqualified disbelief, 10 indicated neither belief nor disbelief, and twenty indicated total unqualified belief². This rating could not be used to meaningfully compare different individuals, nor does the same score in different categories suggest an equivalent level of belief. For example, the authors would propose that a score of 20 for belief in the power of prayer has an equivalent relationship to the Gestalt of supernatural belief as does a score of 20 for belief in unidentified objects (UFOs). Similarly, a score of 10 on UFOs might suggest either an open mind on the subject of extra-terrestrial life, or an intermediate level of belief in something supernatural.

The most egregious errors, however, were in the analysis. Salter and Routledge, as well as the previous workers they cited, assumed that their scores represented interval rather than ordinal measures. That is, they assumed that a score of 10 on a particular item represented twice the belief as did a score of 5. There is no basis whatever for this assumption, as their 20-point scale was an arbitrary one. They calculated, however, the means of the scores for each of their eight items (astrology, ESP and so on), an operation which is invalid for ordinal data.

They then tested the hypothesis that amount or field of education decreases supernatural belief by measuring concordance of year or of field of study with the mean scores of the eight items. Their method of testing these hypotheses assumed, for example, that both belief in prayer and in UFOs were, in some sense, equivalent components of supernatural belief, and, therefore, that the scores on each should be concordant. Yet, as discussed, this is an unreasonable assumption. Their failure to find significant Kendall coefficients of concordance could have been as much due to true lack of concordance among the (mean) scores of the various items, as to the absence of trends in these items over years or fields of graduate study.

Finally, the authors made a number of contradictory assertions. For example, they write: "... natural and [sic] biological scientists had the highest mean belief scores and students in the arts ... had the lowest. ... These differences [were] insignificant ...". Furthermore, descriptions of procedure were vague: "Our interviewers were instructed to explain the questions if problems arose", and the authors remark without additional comment: "Cell frequencies do not in every case add to the total because some data were improperly transcribed".

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BOOK REVIEWS

Logical Development

Development of Mathematical Logic. By R. L. Goodstein. Pp. vii+150. (Logos: London, September 1971.) £3.50.

WHEN Boole applied algebraic techniques to logic in 1847, he was thinking of logic in the traditional manner, as the theory of correct inference; and both Frege and Russell also confined their attention to such subject matter when they sought to exhibit logic as the ultimate foundation of pure mathematics. But as mathematical logic entered its classical phase, during the 1930s, other studies were seen to be very much bound up with it, as for example recursive arithmetic. Today we find mathematical logic firmly established as one of the central mathematical disciplines, ramifying in many different directions, for example into mathematics proper, foundations of mathematics, and the theory of computation. Many good books on mathematical logic are now available, written at all levels of difficulty, and varying between complete informality and austere formal rigour of presentation; but it is not altogether easy to get from any one of them an overall view of the entire field. This is precisely what Professor Goodstein's remarkable book provides.

The book begins with four chapters on propositional and predicate logic, treated both by model theory and by proof theory (that is, both semantically and syntactically). But these chapters are not as in most other books, since very many special topics are touched upon, such as Post's theorem on Sheffer functions, intuitionist calculi, natural inference and tableaux, sequent logic and Kripke semantics. There then come four more chapters, devoted respectively to recursive functions, formalized arithmetic, free-variable arithmetics, and axiomatic set theory, with an even greater wealth of special topics—and all this in 150 pages, which include a well chosen bibliography!

It seems to me that beginners would tend to find much of the book hard, and perhaps rather bewildering, since so many big topics are reported on in summary fashion, accurately indeed, but without much explanation. To the

reader who already has some initial knowledge of the whole field, however, the book could prove invaluable, both as a means of orientation and as a guide to further topics that it is important to learn something about. Anyone who worked through the book systematically, reading up each topic in turn with the aid of the notes and bibliography, would find himself committed to an extended course of study; but by the end of it he would really understand what modern mathematical logic, taken in an all-embracing sense, is about. He might not have studied automata theory, say, and perhaps a few other things, but his reading would have been thorough and productive.

G. T. KNEEBONE

US Science

Science in American Society: a Social History. By George H. Daniels. Pp. xii+390+x. (Alfred A. Knopf: New York, May 1971.) \$10.

THIS well written and amply documented book is largely about the period before 1900. Only the last and part of the penultimate chapters cover the present century, making this another case of *Hamlet* without the Prince. The time focus is all the more regrettable because of the promise of the subtitle and the author's politely polemical preface, a promise largely unrealized even in the treatment of the earlier period. Promise and performance do not match; why they do not match endows this book with some historiographic interest.

Daniels bluntly characterizes much of the writings in the history of science as "celebratory", presumably of great men and great achievements or as being an idealized, if arid, analysis of scientific ideas. Science as a human activity, Daniels insists, occurs within a national ideological framework, and is best viewed as a part of a national culture. The part influences the whole, while the whole influences the part. While Daniels stops short of asserting that science as practised in one nation is inevitably different from the practices in another nation, the book is definitely in the old tradition stressing America's historical uniqueness.

Among historians of science at present is a rather lively stirring about the shape of the subject. Voices are heard asserting the importance of factors outside the internal flow of scientific data and concepts. Coming to mind immediately is the recent spate of articles on the origins of the Royal Society. In this rather academic discussion the United States is unique, for only there, to my knowledge, do we find a substantial body of historians investigating the sciences as part of the national experience, rather than particular disciplines. These historians—at least twenty-four come to mind—are, for the most part, not close to their colleagues in the history of science proper, being concerned with governmental policies, scientific organizations and informal groupings; the applications of science to medicine, agriculture, and technology; the relations of scientists with other groups in the United States; and (recently) the socioeconomic origins of the scientific community. They are best described as general American historians trying to integrate the sciences into the national history.

Daniels seems to belong to this school; parts of the text are explicitly derived from such writings, including his own contributions. But the volume is far from social history. It is, rather, from a different genre, that of American intellectual history. The method is closer to Perry Miller, Henry Steele Commager or Ralph Gabriel than to Marc Bloch. What we have here are idealized abstractions—Newtonianism, Darwinism, the Progressive Era, the Jacksonian Spirit—around which Daniels arrays what scientists and non-scientists said about science. Although the genre is worthwhile, it hardly constitutes a social history. Only his nationalistic focus prevents Daniels from realizing that his practice is closely related to many writings of conventional historians of science. A real social history of science is sorely needed. Large stretches of the literature are either too close to a pedantic antiquarianism or too idealized. Whatever the relationships between the content of science and the ambient milieu, we sorely need a full picture, not a

partial view, of the totality of scientific activity.

What strikes an American reader is how Daniels, in spite of his virtues, runs into trouble because programme and practice fail to match. Daniels strongly insists—too strongly in my opinion—that a democratic culture concept in the pre-Civil War years hindered professional growth by an anti-elitist, egalitarian view of science. By the Progressive Era, the expert is in the saddle for reasons left unclear by the author. Since his method inclines to neat intellectual dichotomies, Daniels equates uniformitarians with partisans of natural selection and catastrophists with opponents of natural selection, a gross oversimplification of the situation in the United States and Britain. Being conscious of intellectual positions, Daniels cites chemists in post-Civil War America as leaders in the pure science ideal drive. A social history would have noted that many, perhaps most, chemists of that day were in applied endeavours. Since intellectuals wrote about the survival of the fittest, Daniels assumes businessmen literally believed in this competitive ideal, even though he himself cites the contrary views of Andrew Carnegie. Most American historians today note that many American businessmen tried their best to minimize competition by forming trusts or engaging in tacit price fixing. Daniels is unaware of recent work casting doubt on the view that the Social Darwinists believed in the jungle bloody survival of the fittest.

A sprinkling of errors indicates a rather careless handling of mere facts, even for intellectual history. Cartier did not explore western Canada. Benjamin Rush studied chemistry at Edinburgh to get a medical degree, not merely to aid industry. The Smithsonian was not a "museum of public entertainment" in its early years. Two different dates are given for the start of the important Darwin-Gray correspondence. Darwin was by no means one of the first scientists to appeal to nature rather than to logic. There never was a Federal Bureau of Agriculture, the term "Department" being used even before cabinet status was attained. Simon Newcomb never "headed a government observatory". John Wesley Powell fell in the early 1890s, not the late 80s. The Science Advisory Board of 1933 was not advisory to the Tennessee Valley Authority. Frank B. Jewett was president of the National Academy of Sciences, not the AAAS. While these are perhaps pedantic quibbles in terms of that splendid abstraction, a national ideological framework, yet they are the stuff from which a true social history of the sciences in America will some day emerge.

NATHAN REINGOLD

Substitution Reactions

Free Radical Substitution Reactions. By K. U. Ingold and B. P. Roberts. Pp. viii+245. (Wiley: New York and London, August 1971.) £5.75.

THE authors of this volume seem to have found considerable difficulty in finding a suitable title. Having chosen *Free Radical Substitution Reactions*, they take justifiable pains to make clear what is not to be found in the book. The subtitle brings the prospective reader much nearer to the real content, which is concerned with S_H2 reactions. If the reader is still mystified the preface makes the position quite clear in the statement that bimolecular homolytic substitution reactions involve the attack on an atom in a molecule by an incoming radical to bring about replacement of a second radical originally bound to the atom. Further, since the majority of the chemical elements are multivalent, the atom under attack is not a terminal one. Ten chapters deal in turn with elements of group IA, groups IIA and B, group IIIA, group IVA, group VA, group VIA, group VIIA, transition elements, rare earth elements, and finally group O elements, for which, incidentally and not surprisingly, no example of an S_H2 reaction is as yet known. The chapters vary considerably in length and, as is to be expected, reactions at the oxygen atom receive the most attention. Reactions at carbon, sulphur, phosphorus and the metals tin, mercury, cadmium, zinc, magnesium, and aluminium are also reported at some length. The presentation of the subject matter is logical and precise to the extent that the reader should be able quickly to locate the information he wants and for this reason a subject index is not included.

The subject matter concerns bimolecular homolytic processes at multivalent atoms involving attack on interior or non-terminal atoms. Such reactions may be synchronous or stepwise, depending in each case on the properties and behaviour of the initially formed adduct radical. Where appropriate, stereochemical considerations are fully discussed. Reactions involving metals, for example, magnesium, mercury and tin, frequently have important implications for preparative processes. In some of the reactions discussed the existence of an S_H2 reaction is by no means firmly established, as is in fact made quite clear by the authors themselves, and there is frequently quite a divergence between the behaviour of reactions at atoms within the same group, for example, nitrogen and phosphorus. The wide occurrence of S_H2 reactions at oxygen is not unexpected. Such processes have attracted much attention largely as a result of the use of peroxides as initiators in polymerization studies and other

free radical processes. Reactions at the sulphur atom have also received wide study in particular with compounds containing the relatively weak sulphur-sulphur bond. The subject matter is treated with a measure of critical insight into mechanisms and perhaps one of the most interesting features of this volume is to be found in the revelation of the diversity of behaviour which is to be found in the reactions which can be classified as S_H2 processes.

This volume makes a useful addition to the rapidly growing literature of free radical chemistry and it is particularly acceptable because it brings together for the first time a wide range of information, which will become of increasing interest to both academic and industrial chemists.

D. H. HEY

Mathematical Genetics

Probability Models and Statistical Methods in Genetics. By Regina C. Elandt-Johnson. Pp. xviii+592. (Wiley: New York and London, August 1971.) £11.75.

THIS book covers the standard topics of mathematical genetics, such as segregation ratios, gene frequencies in populations, genetic correlations, the effects of selection, inbreeding, linkage, mutation, assortative mating and so on. It also includes a chapter on the theory of incompatibility of transplants, a field in which Professor Elandt-Johnson has herself done some useful work. The author states that the book is intended for biologists with only a minimum knowledge of mathematics and statistics; about six of the nineteen chapters are taken up with an explanation of standard statistical theory and practice, chiefly from the Neyman-Pearson point of view. The references listed in the book provide a very helpful guide to further reading and to original papers.

As might be expected from this author, the book is (with a few exceptions) written most carefully and lucidly, and with an emphasis on exact definition, though difficult proofs are omitted. The book also usefully explains some of the practical methods of analysing genetic data (especially in human genetics).

Professor Elandt-Johnson points out from time to time some of the snags and qualifications, and notes that the conclusions only follow when the original assumptions are valid. However, these necessary disclaimers are not always very prominent. One wonders what a reader new to the subject will make of the (perfectly correct) qualification that the theory of confidence intervals does not enable one to draw any conclusions from any particular sample. In his investigation he will collect many samples, and will want to draw conclusions from

them; a qualification of this kind must either seem quite baffling, unless its motivation is explained carefully, or it will simply be ignored.

Again, Professor Elandt-Johnson does not point out the very different reliability of the various methods. In theory, the Hardy-Weinberg law should scarcely ever hold in real populations, since there are always disturbing factors. In practice, it almost always holds, with sufficient accuracy for any practical purpose. In contrast, the elegant theory of ascertainment probability for a rare genetic condition must be scarcely ever applicable to real data. For it is based on an assumption that all affected individuals have, independently of one another, the same probability of being a proband (that is, of coming directly to the notice of the investigator, excluding cases found only because they are relatives of some other affected individual). It is very difficult to think of a reasonable and practicable method of sampling with the property that two affected brothers have independent chances of being probands in this sense. (Random sampling is not practicable here.) For example, one commonly used sampling procedure will be through enquiries made to medical practitioners; but brothers, especially if they are young, will often have the same physician. Moreover, failure of this assumption will quite appreciably affect the accuracy of the conclusions obtained. The perfection of the book, in which the subject is mostly presented neatly and tidily in best Sunday dress, also conceals the fact that real life is not always so perfect; populations are heterogeneous, genetic conditions do not always follow Mendelian ratios, estimates of mutation rates are inconsistent, samples are heavily biased, and major theoretical problems remain unsolved or controversial. For these reasons the book must be read with caution and with awareness of reservations. Subject to this, it represents a useful exposition of some of the most important parts of mathematical genetics.

CEDRIC A. B. SMITH

Liquid Scintillation

Liquid Scintillation Counting. Edited by A. Dyer. (Symposium at University of Salford, September 1970.) Pp. vii + 133. (Heyden: London, New York and Rheiner, July 1971.) £4.60; \$12.

THE principle of liquid scintillation counting is deceptively simple. Its practice has become remarkably complex. A specimen labelled with a β -emitter, usually tritium or carbon-14, is introduced into a fluorescent organic solution, and the scintillations induced in the solution by the β -particles are detected by a pair of photomultipliers, operating in

coincidence to minimize background noise. With the development in recent years of many increasingly sophisticated automatic counting instruments, liquid scintillation counting has become established as the basic technique for the radio-assay of biological specimens.

The complexities arise from the variety of biological materials and their physico-chemical properties; the numerous sample preparation techniques and solubilizers which are used to incorporate them into the solution; the many different scintillator solutions which are used, and the intricate sequence of events which constitutes the scintillation process. To quote Dr Kalbhen's concluding remarks at this symposium: "For each variation in solvent, solute and sample preparation techniques, it is necessary to recalibrate the liquid scintillation counter to optimal counting conditions. It has become quite impossible to compare quantitatively counting results from one laboratory with those from another". In spite of these limitations, which may ultimately be overcome by the adoption of standardized sample preparation methods which convert all biological materials into the same combustion products, satisfactory liquid scintillation counting methods have been developed for the routine radio-assay of a very wide range of biological materials.

The thirteen papers in this slim volume were originally presented at a two-day symposium at the University of Salford. Topics discussed include chemiluminescence as a problem and as an analytical tool, the emission spectra of liquid scintillators, the determination of the activities of carbon-14 and electron-captive nuclides, and a new gelifying agent for specimen incorporation. Three papers are devoted to the use of computer techniques for data processing and quench correction, and two deal with specific biological applications to thyroid cell DNA, enzymes and drug actions. Two papers on scintillations in liquid helium and the design of a liquid helium neutron polarimeter seem strangely out of context. The contents of the volume seem to be too diverse to appeal to anyone who is not already a specialist in the subject. J. B. BIRKS

Nuclear Reactions

Nuclear Reactions and Nuclear Structure. By P. E. Hodgson. Pp. xii + 661. (Clarendon: Oxford; Oxford University: London, October 1971.) £14.50.

PETER HODGSON is a physicist's physicist, a man poised half way between the theoretical and experimental world, who provides the necessary bridge between the desk bound and bench bound nuclear physicist. Although truly a theoretician, Hodgson

still hankers after his experimental beginnings as a research worker and with such a background he is well suited to write a book such as this that aims particularly at the experimental physicist. It is this background that perhaps makes this book the eminently readable book that it is—a rare quality in a volume that is a comprehensive survey of a kinetic subject such as nuclear reaction theory.

Nuclear Reactions and Nuclear Structure comes eight years after the author's first book in this field, *The Optical Model of Elastic Scattering*, also published by the Clarendon Press. Not unnaturally there is a deal of common ground covered but these sections have been completely revised with references included up to 1971. In 1963, Hodgson treated only the scattering of nucleons but now he turns his attention to the full complexities of nuclear reactions as well without, however, going into details of how gamma ray data can aid in unravelling the details of reaction mechanisms. He says in the introduction that the subject matter covered is a matter of his own taste and interest. It is thus not surprising that in this book we find a most comprehensive and up to date treatment of the optical model and distorted wave treatment of nuclear reactions. It is unfortunate in a way, but certainly not so in another, that such a book as this gets dated very quickly, and one has only to compare *The Optical Model of Elastic Scattering* and the present volume to realize how fashion has changed in the field of elastic scattering in the past eight years.

What sets Hodgson's book apart is his frequent comparisons between experiment and theory, exemplified by figures taken from published articles. This will be welcomed by the experimental nuclear physicists who often have to suffer books that make no attempt to marry theory and experiment. Hodgson also makes no attempt to involve the reader in mathematical calculations and, as he rightly points out in the introduction, the techniques of mathematical manipulation spread over several chapters would be indigestible to the reader. The experimenter, of course, is more concerned with the implications of how the theoretical calculation fits his results than with the subtleties of Racah algebra.

There is no doubt that all experimental physicists working in the field of nuclear reactions should have, and indeed will want, a copy of this book. It is unfortunate that the price will make it improbable that they can. It is a sign of the times that whereas *The Optical Model of Elastic Scattering* cost £1.50 for 211 pages, the present book costs £14.50 for 661 pages, a somewhat disproportionate increase.

ALUN JONES

Fossil Mammals

Early Mammals. Edited by D. M. Kermack and K. A. Kermack. (Supplement to the *Zoological Journal of the Linnean Society*.) (V.50.) Pp. xiv + 203. (Academic: New York and London, September 1971.) £5.30; \$15.50.

The Age of Mammals. By Bjorn Kurten. Pp. 250. (Weidenfeld and Nicolson: London, October 1971.) £3.50.

MAMMALS had already passed through two-thirds of their evolutionary history before the so called Age of Mammals began, but knowledge of the Mesozoic mammals is very scanty. In recent years, however, there has been a considerable revival of interest, stimulated by the discovery of new material, and the study of Mesozoic mammals is now one of the main growing-points of vertebrate palaeontology. *Early Mammals* is a collection of papers given at a symposium arranged by the Linnean Society in June 1970. It provides an excellent survey of the state of knowledge at that date, and should be useful to students as well as to research workers.

In view of the nature of the fossil material it is natural that most of the papers are concerned with teeth and jaws. J. A. Hopson describes the replacement of the teeth in the cynodont *Diademodon* and discusses the origin of the mammalian system of tooth-replacement; R. G. Every and W. G. Kühne interpret wear-facets on teeth in terms of "thegosis", a mechanism of sharpening the cutting edges; A. W. Crompton interprets the same facets in terms of occlusal relations, in a well illustrated discussion of the origin of the tribosphenic molar. Other papers describe new material, again consisting of jaws and teeth: J. R. E. Mills on the teeth of *Morganucodon*, B. Krebs on dryolestid mandibles from Portugal, W. A. Clemens and P. M. Lees on Early Cretaceous mammals from England, B. H. Slaughter on Albian mammals from Texas and R. C. Fox on Campanian mammals from Alberta. Only one paper deals with any aspect of skull structure: this is by K. A. Kermack and Z. Kielan-Jaworowska, who compare the brain cases of recently discovered Mongolian Cretaceous multituberculates with those of *Morganucodon* and the present-day monotremes. It is a pity that it was not possible to include at least a preliminary description of the skull and skeleton of *Morganucodon*, which have been under study for some years. In an interesting paper W. A. Clemens speculates on ecological and zoogeographical aspects of mammalian evolution in the Cretaceous, including the yet unsolved problem of how marsupials got into

Australia. Finally, G. G. Simpson, whose monographs of 1928-29 form the foundation of all subsequent work on Mesozoic mammals, gives a valuable critical survey of this developing field.

Only when we reach the Cainozoic does it become possible with some degree of confidence to visualize the mammals as living animals. In *The Age of Mammals* this is what Dr Kurten has set out to do. Writing in a very readable style, and avoiding technical terms as far as possible, he deals in turn with each epoch, describing the geography, climate and vegetation, together with the principal deposits in which fossil mammals occur. Stratigraphical correlation tables and palaeogeographical maps are provided. Against this background the mammals are described in sufficient detail to fit them into their environment. The reader is given a vivid impression of the successive phases of mammalian evolution during the past sixty-five million years, and an indication of the nature of the evidence on which the story is based. Some of the more interesting birds and reptiles are also treated. The book is well illustrated by sixty-seven line drawings and eleven plates by Margaret Lambert depicting life reconstructions of a wide range of fossil forms.

The Age of Mammals is not a textbook but an imaginative synthesis which should provide valuable background reading for students of zoogeography and mammalogy as well as vertebrate palaeontology. As a synthesis it also has interest for the specialist, though inevitably he would disagree with some of the details. There are occasions when the author allows his imagination to run rather far from the evidence: because the teeth of *Planetotherium* resemble those of the modern colugo it does not follow that it was a glider. The list of references is rather short, and there are several instances where one is left to guess at the source of information. While applauding the attempt to avoid technical terms, the use of unfamiliar English names for fossil groups sometimes leads to obscurity: for example, the term "thunderbird" is introduced on p. 171, but not till p. 183 is it revealed that the author means the Phorushacidae. Another minor criticism is that the palaeogeographical maps do not always agree in detail with the descriptions in the text.

Nevertheless, Dr Kurten has succeeded in making the fossils live again. The book is full of vivid images: we can see herds of palaeotheres visiting their selected water-holes, a pantodont defending itself with its heavy paws, a mammoth using its curved tusks to scrape the snow off grass. Whether these things really happened we do not know, but we do know that fossils were

once living animals. Anyone who thinks that palaeontology is a dull, mind-narrowing subject ought to read this book.

P. M. BUTLER

Anti-antibodies

Human Anti-human Gamma-Globulins: Their Specificity and Function. (Proceedings held in Lund, October 1969.) Edited by R. Grubb and G. Samuelsson. Pp. xii + 227. (Pergamon: Oxford, September 1971.) £6.00.

IN recent years, immunologists and geneticists have come to rely heavily on the properties of anti-antibodies. Studies of inheritance of genetic markers of immunoglobulin molecules, synthesis of these proteins at cellular level and the phenomenon of allotype suppression induced in rabbits and mice treated during foetal or perinatal life are all based on the use of anti-antibodies. This book, however, contains only a few papers dealing with these topics; the chief concern of the symposium held in Lund was the discussion of the origin, function and effect of anti-antibodies. Whether this aim was achieved during the meeting, and also whether the participants found the discussion informative, is difficult to say. In my view, however, the published proceedings fail to provide the reader with much valuable information. One reason is that the majority of the papers published in the book are "in abstract form only, as most of the work is already in the process of publication elsewhere". This means that out of the five papers included in session 5 dealing with the presence of immunoglobulin molecules on the surface of lymphocytes, three are no more than two pages long and the results have already been published *in extenso* in scientific journals. One of the few long papers published in the book also appeared recently in an immunological journal.

I was particularly disappointed to notice that the special lecture under the intriguing title of "Foetomaternal histocompatibility in toxemia of pregnancy" was summarized in three and a half pages, of which three tables and a figure comprised a major portion. Finally, the English of some of the papers is rather poor and the meaning occasionally obscure. It should also be mentioned that the title of the book is rather misleading, since many papers discuss the function and the properties of anti-antibodies which are neither of human origin nor directed against human γ -globulin.

The book, of course, contains some original and informative data; particularly interesting is the work of Speiser and collaborators on the transient nature of anti-Gm which appears during childhood.

M. ADINOLFI

CORRESPONDENCE

Alice Economics

SIR,—We feel that you have failed to understand the issues involved in continued economic growth (*Nature*, 234, 2; 1971). It is undeniable that pollution has accompanied economic growth. It may be that economic resources are required to stem the effects on the environment, but before this can be brought about a whole new political atmosphere is needed: our economic efforts must be redirected. Much of the economic effort in modern industrialized communities, such as the EEC, is invested in the production of non-essential consumer goods, aerospace and defence technologies, and other areas where raw materials are consumed almost unthinkingly and where attendant pollution problems are solved, if at all, only as an after-thought.

The industry of the future should be one in which a much greater proportion of the materials used will already have been recycled many times. It should be manufacturing items which are more directly applicable to the world's problems, such as medical goods, birth control devices, agricultural materials, and housing materials. The need for these goods is mainly in poorer countries. The required revolution in the foreign aid and internal economic policies of the rich countries will not be achieved without a radical change in political atmosphere, and we share Professor Scorer's disappointment that no mention of these points was made in the EEC debates.

It is indeed no accident that the richest nation is the most worried about pollution, since it has considerably more than the rest of us, as a result of greater economic advance, and is feeling the effects earlier than most. In pollution terms, and in terms of *per capita* use of natural resources, one American has a far greater impact than, for example, one Indian. Also, many American citizens are aware of the continuing failure of their political leadership to deal with these problems, and do not share your blind faith that all will turn out right in the end.

What you ignore is that we live in a world which has only a limited quantity of raw materials and can only support a finite population. The plain fact is that the world could not support even its present population if everyone shared the American standard of living: if we

wish everyone to be decently fed and housed, somebody has to be prepared to give. That includes us.

Yours faithfully,

C. J. BOLTON
J. E. CORDWELL

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Alice Economics

SIR,—I find the editorial attitude expressed in Professor Scorer's letter to *The Times* distressing; and, worse, bigoted. If he is irresponsible in his "environmentalist" attitudes, so indeed are you with your "growth is a prerequisite to improvement" attitude. Do you have a connexion with economists? It appears to me that only they of our ideological dinosaurs continue to put all their eggs in the long since worn out basket of required economic growth via an expanding population. Surely economic growth can also be achieved with a static or even a decreasing population?

Overall there is perhaps only one obvious fact, one which you choose to ignore, and which is the basis of Professor Scorer's letter. This is the need for a fundamental change of some sort. To a mathematician, or indeed any logically inclined person, the exponential curve of population growth can have only one answer, and that is change. The change may be controlled or cataclysmic, but change there will be.

Your comparison of our small and already overcrowded island with the USA (some four times the population in around forty times the area) is ridiculous. That country, with present-day technology, is already capable of feeding its estimated population for the year 2000 and beyond, while our population has already outgrown our own food supply. Indeed, even India, with around eight times the population in twelve times the area, is better placed; when the pressures arise, we shall be among the first to experience them.

Your dismissal of the pollution problem on the grounds of lack of specificity is irresponsible. More worrying is your lack of awareness that the decrease in fish landings to which you refer is itself a form of pollution. Pollution by taking needs to be considered with pollution by dumping.

The Kansas dust-bowls were not produced by the dumping of dust.

Your patronizing attitude to our poorer neighbours must irk them in the extreme. Must they continually rely on aid based on a fraction of our growth? Again a mathematically (and historically) unacceptable model in the long term.

May I say finally that I already find the pressures of today's society bearable only with difficulty, and that I take Professor Scorer's ideas seriously enough to wonder if I wish to take part in your rich and sterile utopia with its increasingly (and necessarily) controlled overpopulation.

Yours faithfully,

I. A. ELLIS

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Ethics for Authors

SIR,—As editors of a monograph series published by a well known university press, we have each had recently the following experience. A competent scientist asks us to consider publishing a book which he has on hand. We reply showing interest, and negotiations begin, involving the assessment of a synopsis and sample chapters, a check on the existing literature, and advice to the press to publish. Improvements of style and content are suggested to the author, and a formal contract is prepared. This is a lengthy procedure and may take many months. We are then told that the finished book has been accepted by another publisher, with whom, in fact, the author was simultaneously negotiating.

In the selling of a house such conduct is usually regarded as dishonourable, if not quite actionable. In the jungle of commercial publishing one must, no doubt, be prepared for such dishonesty. But in the production of specialized scholarly works this is unethical behaviour, not at all in the interests of authors themselves.

It is true that we are paid as editors in proportion to the success of the books that we get into print. Some unscrupulous editors and publishers make a quick profit by accepting every manuscript, without question or revision and wax rich on high-priced sales to libraries. But most scholarly editors do not do this sort of job solely for monetary

gain: they regard their labour as a general service to the scholarly community, to maintain high literary and scientific standards, for the benefit of their colleagues as authors and as readers.

Our complaint is at the selfish and frivolous waste of our professional time and effort in the name of "free competition". Not nearly enough trouble is taken by most scientists to improve the quality of the books they must read: it is scandalous that the little we do should be spent thus fruitlessly. It is poor consolation, incidentally, to observe afterwards that the author has not hesitated to benefit (without acknowledgment) by the improvements we have proposed.

We also believe that the credibility of scientific publications depends upon an agreed and orderly framework, in which well qualified editors and reputable publishers respect themselves and one another. The margins of technical book publishing are not so elastic as to allow wide variations in the real terms that can be offered to authors. The ultimate financial return on a book depends on much more imponderable factors than the apparent royalty percentage or the quality of the burgundy at a tax deductible lunch. A good book can easily be published and an author does much better by bargaining hard and honestly with almost any single good publishing house than by "shopping around".

Some people do not seem to have thought this out, and fall for the fast buck. Let us spell it out to them. They know well enough that they must not submit the same research paper simultaneously to two different journals. We suggest that the behaviour here reported must be considered a comparable breach of the unwritten ethical code of the scientific community.

Yours faithfully,

M. M. WOOLFSON
J. M. ŽIMAN

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Viral DNA Integration

SIR,—In a review article "Vintage Year for Tumour Virology" (*Nature*, 233, 28; 1971) John Tooze states: "and the recent experiments of Wall and Darnell (*Nature New Biology*, 232, 73; 1971) dispel any doubts about the integration of polyoma (actually SV 40) virus DNA into host cell DNA". Recent experimental evidence throws new light on this situation (Gelb *et al.*, *J. Mol. Biol.*, 57, 219; 1971). Because of it, there is to my knowledge no published evidence which conclusively demonstrates the integration of SV 40

DNA into the DNA of the transformed host cell. Gelb *et al.* have recently shown that host specific SV 40-like sequences exist in non-transformed cell green monkey and mouse DNAs. About one-half copy of host specific SV 40-like sequence is present in each cell. Published experiments designed to demonstrate the integration of SV 40 into transformed cell DNA have relied on the reaction of SV 40 C-RNA (RNA made *in vitro* from SV 40 DNA) with transformed cell DNA which had a molecular weight much higher than SV 40 DNA (Sambrook *et al.*, *Proc. US Nat. Acad. Sci.*, 60, 1288; 1968). It was assumed that any reaction of C-RNA was with virus specific SV 40 sequences, which had been integrated into the host cell DNA. However, the existence of host specific SV 40-like sequences in DNA from transformed cells complicates the interpretation of these data. It is not known whether the C-RNA reacted with host or virus specific SV 40-like sequences. The interpretation of Sambrook *et al.*, that SV 40 DNA is integrated, rests entirely on the greater degree of reaction of SV 40 C-RNA with high molecular weight SV 3T3 cell DNA than with PY 3T3 high molecular weight DNA. This result could be the consequence of: (a) the integration of virus specific SV 40 sequences in the host DNA, or (b) the differential replication in SV 3T3 cells (and not in PY 3T3 cells) of the chromosomes which contain the host specific SV 40-like sequences.

The data of Lindberg and Darnell (*Proc. US Nat. Acad. Sci.*, 65, 1089; 1971) and Wall and Darnell are also difficult to interpret for the same reason. It is not known whether the large RNAs they detect, which contain both SV 40-like and host specific sequences, arose from virus specific SV 40 sequences or from the host specific SV 40-like sequences which are present in non-transformed cells.

In summary, I do not believe that the virus DNA integration into transformed cell DNA has been proven.

Yours faithfully,

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Library Optimum

SIR,—In his recent article¹ B. C. Brookes propounds an ingenious mathematical framework to determine which periodical volumes a library should hold. He is careful to point out that the selection will need regular review and revision, in case the value of the ageing factor a or the contents of the Bradford set change from year to year. There is as yet very little experimental evidence on the consistency

of either. Such limited evidence as there is suggests that the ageing factor is reasonably constant. But the position of the Bradford set is less satisfactory. The Nature Conservancy librarians (J. M. Weingott and S. M. Penny, unpublished) have lent me a list of titles cited in the *Journal of Ecology* three or more times in 1955–56, and a similar list for 1965–66. There are 150 periodical titles in the two lists, but only forty-two (28%) appear in both. Of the thirty-three titles cited nine or more times in either year, only eight (25%) attained that level in both, and twelve were cited less than three times in the other year. The Kendall rank correlation coefficient between the two years is 0.18 and not significant.

There is another major practical problem. The article assumes that the data analysed to obtain ageing or utility factors and Bradford sets are valid parameters of the relative value of the literature to the readers. There is no mention of the type of data to use. The reader who sought guidance from the earlier literature cited would find practical techniques described in which analyses of citation frequencies are used to calculate utilities discussed in terms of library use. Krauze and Hillinger² have discussed the difference between citations in one article and future citations to that article. Their work implies a more complex relation between a and u than Brookes suggests. In any case, the validity of citations for forecasting library consultations remains unproven, and there are *prima facie* reasons why the relationship is not necessarily close. For example, one item in a list of references is often intended to lead to a chain of earlier papers. Again, each citation represents an author's selection from a wider group most of which he has consulted in a library. In neither case is there any inherent reason for similarity of age distribution or of pool of titles between the list of citations and the items read by the author or his readers.

Most of the practical studies of citations or library use have so far been based on the relation between frequencies and age or title, without considering the number of items available for reference. But, to be useful as parameters of the relative value to scientists of groups of volumes, the data must be presented as the number of references per available item, and not as the numbers from groups of differing size. The need to correct "obsolescence rates" for the fact that there is much less of the older literature to cite or read is becoming generally recognized. When the appropriate corrections are made, it has been shown³ that in some library contexts the older literature can be more heavily used than the younger. In all calculations based on Brookes's utility concept it is therefore essential that the utility factor u be derived from an ageing factor a repre-

senting the change in references-per-item (not the crude changes in references) with age. The terms item-consultation decay rates and item-citation decay rates have been suggested³ for suitably corrected factors.

Similar considerations apply equally to the data for obtaining a Bradford set. One citation in 1970 to a periodical first published in 1965 is much more significant than to one first published in 1960 because there are twice as many volumes of the latter available to be cited. Applying a correction to the Bradford sets in the *Journal of Ecology*, to allow both for the age of the periodical title and for an item-citation decay rate of 0.95 (a preliminary value obtained from citations in the same journal), raised the Kendall rank correlation coefficient to 0.25: but this is still not high enough to place much reliance on the predictive value of a Bradford set for ecological literature.

Scientists and librarians would therefore be wise to approach an optimum *P%* library with caution and to check that the data they use for measuring the relative value of parts of their stock are suitable for the purpose and consistent

from one occasion to another. Until they have done so they should not take any irrevocable decisions on the basis of Bradford sets or ageing factors.

Yours faithfully,

A. SANDISON

*National Reference Library of
Science and Invention,
Holborn Division,
25 Southampton Buildings,
London WC2A 1AW*

¹ Brookes, B. C., *Nature*, **232**, 458 (1971).

² Krauze, Tadeusz K., and Hillinger, Claude, *J. Amer. Soc. Inf. Sci.*, **22**, 333 (1971).

³ Sandison, A., *J. Doc.*, **27**, 197 and 189 (1971).

Sex Discrimination

SIR,—We were startled to read in your issue of October 29 (*Nature*, **233**, xxii; 1971) an advertisement, placed by the Australian Atomic Energy Commission, describing a research post and ending with the statement "Female rates slightly less than male rate quoted". The fact that sex discrimination is still an official policy of the Australian government does not,

in our opinion, absolve a private journal such as yours from the responsibility not to abet discrimination based on race, national origin, political or religious belief, or sex. We presume, for example, that *Nature* would not now accept advertisements that were discriminatory with respect to colour or religion. We look forward to a prompt and public statement by *Nature* of a new nondiscriminatory advertising code.

Yours faithfully,

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Obituary

Dr Colin Cadman



COLIN HOUGHTON CADMAN, plant pathologist and Director of the Scottish Horticultural Research Institute, Dundee, died on September 27, aged 55.

After graduating from Liverpool University with First Class Honours in Botany he first worked at the Scottish Plant Breeding Station, Edinburgh, on the genetic control of the reaction of potato plants to virus infection. This work, which formed the basis of his PhD thesis, was the origin of his interest in plant

viruses, and he devoted the rest of his productive research career to their study.

In 1943 the Scottish Raspberry Investigation, directed from East Malling Research Station, was set up at Dundee and Cadman became its resident pathologist. The main aim of this unit was to tackle the problems posed by the degeneration diseases of the raspberry, a crop more intensively grown in the area than anywhere else in the world. During the next eight years, by shrewd observation and simple experiments, he differentiated and identified many new viruses affecting raspberry and showed that some were spread by aphids. He began to propagate healthy stocks and became the foremost expert in raspberry viruses.

When the Scottish Horticultural Research Institute was founded in 1951, he became the head of its Plant Pathology Department and his research entered its most imaginative period. He discovered that a virus could be transmitted experimentally to herbaceous test plants by inoculating them with sap from raspberry plants affected by the important leaf curl disease. This led to the recognition of a group of viruses which cause ringspot symptoms in plants, have wide host ranges including numerous weed and crop species in many countries, and which spread through the soil. Following the American report that grapevine fanleaf virus has a nematode vector he showed

that arabis mosaic virus, one of the soil-borne ringspot viruses found in Britain, is similarly transmitted; and that grapevine fanleaf virus can be sap-transmitted to herbaceous test plants and is serologically related to arabis mosaic virus. Other kinds of nematode-transmitted viruses were also found and one, tobacco rattle virus, was consistently obtained from potato tubers affected by sprain, a common disease that had previously defied efforts to determine its cause. A new field of plant virology was opened up and Cadman's laboratory became a centre of international repute for the study of soil-borne viruses.

He also did other pioneering work. He showed how to avoid the effects of substances that hindered the detection of viruses in woody species; he found a virus that was spread between raspberry plants, not by vectors but in pollen; and, independently of German workers, he showed that some isolates of tobacco rattle virus existed in plants as ribonucleic acid that was not protected by a protein coat.

His research having been the main foundation of the scientific reputation of the Scottish Horticultural Research Institute, he became its second Director in 1965. During the next six years he achieved a transformation. Research was reorganized to stimulate scientific productivity, and a comprehensive build-

ing programme started to provide improved accommodation and modern facilities. He fostered closer links with the farming and processing industries, he set up the Institute Association to bring the two together and keep them informed of research results, and he did much to launch the Scottish Nuclear Stock

Association, which was founded initially to propagate the Institute's virus-free raspberry stocks for distribution to growers.

Colin Cadman had a quiet, sympathetic and perceptive but determined nature, and never took his decisions without careful thought. He gave much unselfish

help to younger colleagues, and encouraged them to pursue problems in depth regardless of whether immediate practical applications were likely to result. In private life he was a good field botanist who loved the Scottish hills and was an accomplished cellist. He was not married but will be much missed by many friends.

Announcements

University News

Dr Alan Thompson, University of Edinburgh, has been appointed to the new chair of economics of government in Heriot-Watt University.

Dr M. H. Day has been appointed to the chair of anatomy tenable at St Thomas's Hospital Medical School and **Dr C. D. Marsden** has been appointed to the chair of neurology tenable at the Institute of Psychiatry and King's College Hospital Medical School, University of London.

Professor Richard Lynn has been appointed to the chair of psychology at the New University of Ulster.

Appointments

Lord Orr-Ewing has been appointed deputy chairman of the Metrication Board.

Errata

THE title of the article by V. P. Starr (*Nature*, 233, 186; 1971) should be "Eddy Viscosity and the Solar Rotation".

IN the article "Cyclic Expression of Blood Group Determinants in Murine Cells and their Relationship to Growth Control" by D. B. Thomas (*Nature*, 233, 317; 1971), the abscissa to Fig. 2 should read: "Hours after release of double thymidine block".

Reports and Publications

not included in the Monthly Books Supplement

Great Britain and Ireland

The Science of Botany: From Simple Lore to Social Need. By Professor A. G. Morton. (Inaugural Lecture, 15th March 1971.) Pp. 18. (London: Chelsea College, University of London, 1971.) [168]

Annual Report of the Meteorological Office 1970. Pp. xii+102. (London: HMSO, 1971.) 80p net. [168]

Department of the Environment. Water Pollution Research 1970: The Report of the Water Pollution Research Laboratory Steering Committee with the Report of the Director of Water Pollution Research. Pp. vii+185. (London: HMSO, 1971.) £1.15 net. [178]

Department of Education and Science. On Course Bulletin No. 1: Certificate in Office Studies. Pp. 8. (London: Department of Education and Science, 1971.) [178]

County Councils Association; Association of Municipal Corporations; Urban District Councils Association; Association of Public Analysts. Joint Survey of Pesticide Residues in Foodstuffs sold in England and Wales, 1st August, 1967-31st July, 1968 (second year). Pp. 38. (London: Association of Public Analysts, 1971.) £1.10 (including postage). [188]

Oundle School Natural History Society. Annual Report 1970. Pp. 55. (Oundle, Peterborough: Oundle School, 1971.) [188]

Foreign and Commonwealth Office—Overseas Development Administration. Directorate of Overseas Surveys Annual Report for the year ended 31st March 1970. Pp. 69+8 photographs+9 maps. (London: HMSO, 1971.) £1.20 net. [188]

Ministry of Agriculture, Fisheries and Food. Technical Bulletin No. 24: The Significance of Winter Rainfall Over Farmland in England and Wales. Pp. vii+69. (London: HMSO, 1971.) 45p net. [208]

Central Statistical Office. Statistical News No. 14: Developments in British Official Statistics. Pp. v+26. (London: HMSO, 1971.) 30p net. [208]

Other Countries

Pharmaceutical Manufacturers Association Foundation, Inc. 1970 Annual Report. Pp. 30. (Washington, DC: Pharmaceutical Manufacturers Association Foundation, Inc., 1971.) [98]

Bulletin of the American Museum of Natural History, Vol. 144, Article 5: A Review of the Pre-Pliocene Penguins of New Zealand. By George Gaylord Simpson. Pp. 319-378. (New York: American Museum of Natural History, 1971.) \$2.50. [98]

Mutation Breeding for Disease Resistance. (Proceedings of a Panel on Mutation Breeding for Disease Resistance organized by the Joint FAO/IAEA Division of Atomic Energy in Food and Agriculture and the FAO Plant Production and Protection Division and held in Vienna, 12-16 October 1970. Panel Proceedings Series.) Pp. 249. (Vienna: International

Atomic Energy Agency; London: HMSO, 1971.) 155 schillings; £2.50; \$6. [98]

Commission on Undergraduate Education in the Biological Sciences. Publication No. 32: Guidelines and Suggested Titles for Library Holdings in Undergraduate Biology. Edited by Joan Creager. Pp. iv+65. (Washington, DC: Commission on Undergraduate Education in the Biological Sciences, 3900 Wisconsin Avenue, NW, 1971.) gratis. [98]

The Year Book of the International Council of Scientific Unions 1971. Pp. 241. (Rome: ICSU, 1971.) [98]

FAO—WHO—OIE. Animal Health Yearbook 1970. Pp. 334. (Rome: FAO; London: HMSO, 1971.) £1.60; \$4; FF20. [108]

Environmental Physiology: Nutrition, Pollution, Toxicology, Vol. 1, No. 1, 1971. Edited by J. Clausen. Pp. 1-54. Subscription price: D.kr. 148.00 plus postage D.kr. 12.00 (\$1.50) payable in advance. Price per issue D.kr. 40.00 (\$5.40). (Copenhagen: Munksgaard, 1971.) [118]

Smithsonian Contributions to Zoology. No. 63: Bredin-Archbold-Smithsonian Biological Survey of Dominica—The Dermaptera (Earwigs) of Dominica. By Alan Brindle. Pp. 25. \$0.40. No. 81: The Entocytherid Ostracods of Mexico and Cuba. By Horton H. Hobbs, Jr. Pp. 55. \$0.65. No. 87: Parasitic Copepods of the Family Chondracanthidae from Fishes of Eastern North America. By Ju-shey Ho. Pp. 39. \$0.50. (Washington, DC: Smithsonian Institution Press, 1971. For sale by US Government Printing Office.) [128]

Record of the South Australian Museum, Vol. 16, No. 7: Acarine and other Microfossils from the Maslin Eocene, South Australia. By R. V. Southcott and R. T. Lange. Pp. 21. (Adelaide: South Australian Museum, 1971.) [128]

US Department of the Interior: Geological Survey. Water-Supply Paper 2001-A: Ground-Water and Geohydrologic Conditions in Queens County, Long Island, New York. By Julian Soren. Pp. iv+39+2 plates (Washington, DC: Government Printing Office, 1971.) [128]

Canada: Department of Energy, Mines and Resources. Geological Survey of Canada. Bulletin 174: Geochemistry of Iron, Manganese, Lead, Copper, Zinc, Arsenic, Antimony, Silver, Tin, and Cadmium on the Soils of the Bathurst Area, New Brunswick. By E. W. Presant. Pp. 93. \$2. Paper 71-1: Report of Activities. Part B: November 1970 to March 1971. Pp. vi+139. \$2. Paper 71-18: Secondary Fields of a Vertical Magnetic Dipole Above a Thin Horizontal Layer of Conductive Overburden. By A. V. Dyck and A. Becker. Pp. v+25. \$1.50. (Ottawa: Information Canada, 1971.) [138]

Annual Report of the Inter-American Tropical Tuna Commission 1970. Pp. 127. (La Jolla, California: Inter-American Tropical Tuna Commission, 1971.) [138]

Organisation for Economic Co-operation and Development. Science, Growth and Society: a New Perspective. Pp. 113. (Paris: OECD, 1971.) 10 francs; 77p; \$2.25; 9 Sw. francs; 7 DM. [138]

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